Pharmacotherapy and aggressive behaviour in psychiatric patients

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Farmacotherapie en agressie bij psychiatrische patiënten
(met een samenvatting in het Nederlands)

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Introduction

Introduction

Aggression, and in its extreme form violence, is a complex trans-nosological behaviour frequently observed in psychiatric patients. The complexity of aggressive behaviour is also reflected in different definitions of aggression. The following commonly used definition for aggression measurement was introduced in 1990 by Morisson: "any verbal, non-verbal, or physical behaviour that is threatening (to self, others or property), or physical behaviour that actually does harm (to self, others, or property)"(1).

While there is no general agreement on the definition of aggression, both clinical and academical fields agree that aggression poses a problem in mental health care, which influences well-being of staff and patients and results in high costs (2). Aggressive behaviour does not only affect staff and other patients, but also has a negative impact on the patient, as some studies have shown that aggressive patients are admitted longer on psychiatric wards when compared to non-aggressive patients (3-5).

In the Netherlands, for many years, seclusion has been a frequently used intervention to manage (imminent) aggression. During the last years, the use of seclusion has been heavily debated in response to reports and research indicating that seclusion rates are higher in the Netherlands than in surrounding countries (6). Nowadays, many mental health care institutes have large-scale programmes put in place that aim at reducing seclusion or even banning seclusion all together. An alternative for seclusion, frequently used in surrounding countries, but also in the Netherlands, is (involuntarily administered) pharmacotherapy. In this introductory chapter, we will give a brief historical overview of aggression management, before discussing the currently available knowledge about pharmacological management of aggression.

Dealing with aggressive behaviour through the ages

In the 1980s, some studies suggested that the incidence of aggression in psychiatric wards was increasing, which seemed to parallel tendencies observed in society. Whether there is a real increase of aggressive behaviour, both in society as in mental health care is not clear. Research by Wittebrood and Junger, showed that the observed increase of violence in society might be caused by improved registration (7). Furthermore, historical research shows that aggression has always been an important issue in mental health care and that 'social intolerability' was an important impetus to admission on psychiatric wards. Aggressive behaviour was an important component of such 'social intolerability' (8). Additionally, reforms in psychiatry often were triggered by discontentment with the amount and the way aggressive behaviour was managed. In the next paragraphs the means and measures used to

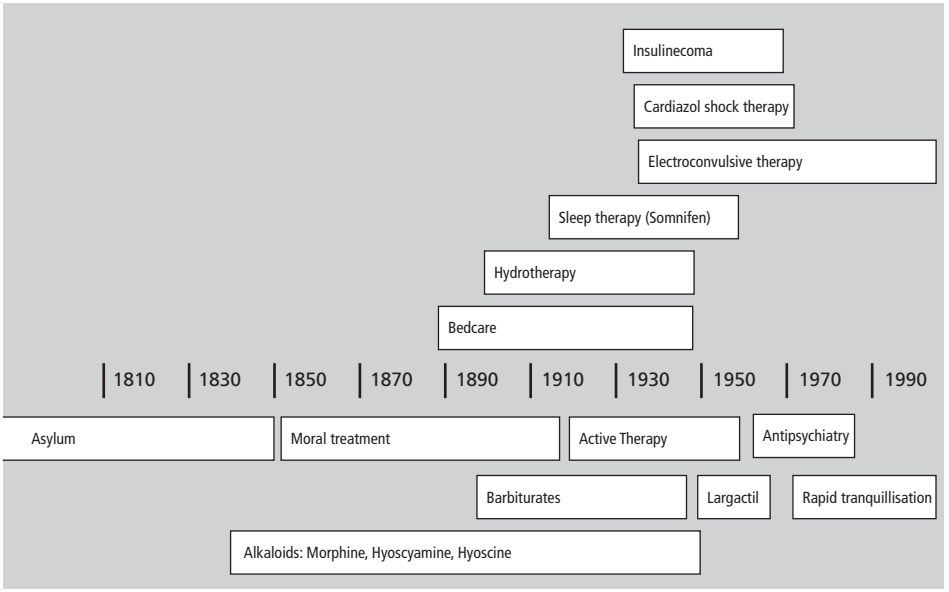

Figure 1 Time table: Movements in psychiatry and used interventions.

manage aggression in psychiatric wards through the years will be discussed, while giving special attention to the situation in the Netherlands (see also Figure 1).
Until the second half of the 18th century, mental problems were not viewed as diseases, which eventually can be cured, but as an abnormality caused by possession (by the devil) or loosing reason thereby becoming animal-like. In institutions, there was hardly any treatment available, only efforts to manage difficult behaviour, including aggression. In the middle ages the "insane" posing danger to others or themselves were put in jail, often naked and in handcuffs. In the 15th century asylums arose in order to give the "insane" a more dignified existence. Aim of these asylums was to shelter the "insane", i.e. to withdraw "idle people" from the community (9). In the asylums –also sheltering old people and orphans- aggressive behaviour of the 'insanes" was also controlled with restraints like handcuffs. Furthermore, small padded cells were in use for solitary confinement.

Then, at the end of the 18th century, in the time of Enlightenment, an optimistic reform movement came. Under the influence of people like Conolly in England and Pinel in France, "insanity" was viewed as a disease, which can be influenced or cured. In these days, personality and behaviour of psychiatric patients were considered to be under total influence of the affected brain. Moral treatment was the way believed to achieve cure or alleviation of insanity. Moral treatment consisted of treating patients in a humane manner and by providing that the hospital was orderly, e.g. by organizing fixed daily schedules and giving timely and appetizing meals. It was during this movement that attempts were made to reduce the use of

restraint. Conolly even thought that restraint would be of no longer use due to moral treatment, treatment considered as (almost) perfect. Besides a certain attitude of the caretakers as described in moral treatment, Conolly also thought the number of attendants to be important. Furthermore, Conolly thought it important to create different pavilions for quiet, semi-agitated and agitated patients. In the Netherlands, in Meerenberg (later on called Santpoort) mechanical restraints were successfully banned after adopting Conolly's theory. Gradually in the rest of the Netherlands, use of physical restraint was reduced. Instead of being restrained, the "restless" patients underwent bed care but also were sent to labour. In those cases in which behaviour was not sufficiently manageable, seclusion and "wet packs" or hydrotherapies were used. Seclusion was not viewed as inhumane as the bodily freedom was hardly restricted. Furthermore, a "single room" approach with an open door policy was tried first before secluding a patient (10). Hydrotherapy, and bed care were inspired by the increasing interest for natural sciences and resulting in a more medical-somatic orientation such as in general hospitals. Hydrotherapy consisted of (forced) bathing with a length varying from hours to days. Administration of barbiturates, e.g. Veronal, was also mentioned in textbooks as a possible intervention in the acute situation. Furthermore, at the end of the 19th century, the alkaloid hyoscine –better known as scopolamine- was introduced. Scopolamine, administered subcutaneously, appeared to better sedate than hyoscyamine which was already in use during the first half of the 19th century for mania (11). Hyoscine (in combination with morphine) was still in use in the 1950s for strong sedation of agitated psychiatric patients, despite the well-known side effects such as hallucinations and depressed mood (11).

Around 1925, besides a medical-somatic orientation, attention was paid to environmental and social factors influencing mental illness. It was also in this time that people realized that bed care and hydrotherapies, originally meant as therapy, were disguised forms of restraint to control disruptive behaviour. In this period, patients were no longer considered to be "under total control" of their mental illness; the opinion arose that only a part of the brain is affected. Agitated behaviour was not longer considered as a cause of illness, but caused by "environmental neglect". In the Netherlands, van der Scheer, introduced active therapy, i.e. fitting labour, and making the patient (more) responsible for his own behaviour (12). This therapy from Germany, was partly a reaction on the very neurological oriented approach of mental illness(12). In order to stimulate own responsibility, nurses used "educational measures" to reward or punish patients according to their behaviour. Seclusion and, after that, prescribing sedative medication were considered last resort if other educational measures had no effect. Although textbooks promoted active therapy, chart review research from Vijselaar [2010] showed that bed therapy was still in use in the 1940s, especially in an attempt to manage difficult behaviour (8). Furthermore, his

findings show that also the somatic therapies like somnifen sleeping therapy, cardiazol, insulin coma and electro shock therapy, arising in the 1920s and 1930s, were not only used for cure or care, but also to manage difficult behaviour. Wet packs in this time were replaced by "strait sheets" which gave patients more space to move and therefore considered more humane and recommended as possible "educational measure".

After the second world war, electro shock therapy was frequently used, not only for cure, but also for the management of agitation and aggressive behaviour(13).

In 1952 there was the introduction of chlorpromazine, an antipsychotic also known as Largactil (= large action). People witnessing the introduction of Largactil -initially used as co-medication for sleep therapy- were impressed by the sudden rest which came over the wards in the institutes, the "Largactil-peace on earth" (13). Schizophrenic patients residing in long-stay wards for restless people became calm and started to participate in daily life in the institute, e.g. by attending therapies. Instead of being sedated, patients became calm and communication with patients was possible. At the same time, it should be stressed that in the Netherlands it took a while before the use of chlorpromazine was widespread. In the Netherlands some "hospital" psychiatrists, for a long time, were sceptical about the effects of psychotropics; they did not see the use of psychotropics as cure but as a way to manage symptoms (11). The lack of enthusiasm has been labelled as a possible reaction on previous therapies like insulin-coma and shock therapies with disappointing results (13) and as a reaction on observed side effects. Despite scepticism, psychotropics were used liberally due to a shortage of nursing staff and in order to maintain manage the agitation on the ward(13, 14). With the availability of parenteral psychotropics, rapid tranquilization technique was developed, a strategy in which antipsychotics or benzodiazepines are administered in a compressed time-frame, titrating dosage against symptoms to control assaultive, hyperactive, and hostile patients (15). Antipsychotics were not only registered for psychosis but also for agitation. An advantage mentioned about the introduction of the antipsychotics, is that people became calm and communication became possible. In the 1960s anti-psychiatry movement appeared. The two principal opinions of this movement were that a) diagnoses were too vague thereby leaving too much room for opinions and interpretations to meet basic scientific standards and b) prevailing psychiatric treatments were considered to be more damaging than helpful.

Much resistance came against the use of restraint in general and the use of medication specifically. Although also in the Netherlands the antipsychiatry movement greatly influenced daily practice, research shows that in the case of (severe) aggression, coercion was still being used. Seclusion seemed to be given preference, although on acute psychiatric wards the use of chemical restraint was still in use (14).

Current practice

Previous paragraphs show that three kinds of interventions have been in use for a long time: interventions restricting freedom of movement (physical restraint and seclusion), chemical restraint and a variety of more behavioural and interactional approaches. Furthermore, history shows that some therapies like prolonged bathing and insulin coma, initially deployed with the idea that they have healing properties, kept on being used even if they appeared to be ineffective. Reason for keeping on using them was to manage difficult behaviour like agitation and aggression. When not taking into account the historical background, it is difficult to understand how caretakers, could be convinced of the efficacy and rationality of such interventions. Nowadays in medicine the importance of evidence-based treatment is highly emphasized. From this perspective preference is given to evidence obtained from randomized controlled trials. The question is whether the current management of aggressive behaviour is more evidence based given the lack of proper studies into the effects of interventions on aggressive behaviour. For aggression in the acute situation, research shows that seclusion and chemical restraint is still in use, if nothing else is working to control dangerous situations clinicians are faced with. On ward level, staff is trained to acquire skills including among others verbal de-escalation techniques. As for the long-term treatment, what has been observed is that aggressive behaviour is associated with increased use of psychtropics. Stolker et al (2001) found an association between aggression symptoms and multiple drug use in a study population consisting of mentally disabled patients (16). Furthermore, on an acute psychiatric ward, medication changes were found to correlate with aggression (17). Finally, studies investigating the use of (oral) as-needed medication on psychiatric wards show that agitation, an aggression-related symptom, is a common reason for administration (18). As far as we are aware of, evidence from randomized controlled trials for these practices is sparse or lacking.

Aims of the thesis

In this thesis we will focus on the pharmacotherapy used by aggressive (in)patients. We aim to evaluate the available evidence for the pharmacotherapeutic management of aggressive behaviour, and investigate whether daily clinical practice is in line with evidence. Furthermore we will attempt to elucidate the reasons for the application of pharmacotherapy for aggressive patients. Current available research suggests that despite a lack of evidence pharmacotherapy is frequently used in clinical practice. A final aim of this thesis is to investigate whether practices in daily clinical practice are effective.

Outline of this thesis

Chapter 2 – Evidence for treatment

Whereas pharmacotherapy plays an important role in guidelines, there are no recent systematic reviews in which the evidence for pharmacological management of aggression is analysed. In this chapter we systematically investigate the evidence for the pharmacological management of aggression in the acute situation (***chapter 2.1***) and the maintenance pharmacotherapy of aggression (***chapter 2.2)***. Furthermore, in ***chapter 2.3***, we aim to gain insight in the generalisability of this evidence to daily clinical practice.

Chapter 3 – Treatment in practice

In this chapter we investigate drug treatment patterns of aggressive psychiatric inpatients compared to non-aggressive psychiatric inpatients. Therefore, the registration of aggression is required. The Staff Observation Aggression Scale – Revised (SOAS-R) (19) is used for this purpose. As this instrument is a quantitative, incident based aggression-scale, there is a risk that underreporting of aggressive incidents occurs. The amount and nature of this possible underreporting is investigated in ***chapter 3.1***.

Medication regimen can be roughly divided into regular medication regimen -medication administrated in defined dosages at fixed time-points as-needed– and as-needed medication regimen –medication administered as required by the nurse on either the initiative of the patient or the nurse self.

Hypothesizing that aggressive behaviour leads to reactive prescribing behaviour, changes in regular medication are investigated in ***chapter 3.2***

The use of as-needed medication by aggressive patients is investigated in ***chapter 3.3***. Furthermore, beliefs of patients and nurses about as-needed medication are investigated in ***chapter 3.4***.

Medication is frequently used in psychiatry, especially for aggressive patients. In the final ***chapter 3.5,*** we aim to investigate how the use of medication affects the outcome of treatment. To make a distinction between a positive and negative treatment outcome, the place to where patients were transferred after admission is used as criterion. Discharge to a less restrictive environment is considered as a positive outcome, discharge to a more restrictive environment as a negative outcome. The association of both aggression and medication use with the treatment outcomes is investigated.

Chapter – 4 General Discussion

Studies will be discussed in a broader perspective in ***chapter 4***, the general discussion.

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2

Evidence for treatment

Chapter 2.1

Pharmacotherapy of aggression in the acute situation: a systematic review

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Adapted from: Richter, D., & Whittington, R. (eds.), Violence in mental health settings: Causes, consequences, management (pp. 173-190). New York: Springer.

Abstract

Objective Aggression is an important issue in mental health departments. Several interventions and coercive measures are used in daily clinical practice to manage aggression. One of the interventions used in psychiatry to manage aggression is the administration of psychotropic drugs. Whereas chemical restraint is frequently used to manage acute aggression, the evidence is scarce. In this systematic review we investigated the evidence for the drugs currently used in the management of acute aggression in a general adult psychiatric population.

Methods We searched Medline, Embase, Psycinfo and the Cochrane library for meta-analyses and randomized controlled trials on the pharmacotherapy of aggression. We excluded those studies referring to specialized psychiatric settings and non-psychiatric settings. Studies were judged to their internal validity and generalizability to daily clinical practice.

Results As well as for antipsychotic agents including haloperidol, droperidol and zuclopenthixol, promethazine as for benzodiazepines including lorazepam and midazolam evidence for effectiveness was found. Study limitations comprised small study populations -which might result in a lack of power to show superiority of one drug above another- short study duration, and poor generalizability to daily clinical practice.

Conclusion On the basis of the evaluated studies and taking into account the study limitations, droperidol appears to be first choice if tranquillisation is required as soon as possible. Furthermore the combination of haloperidol and lorazepam is fast acting and appears to be more sedating than monotherapy. If a calming down effect is more desired than sedating the patient, monotherapy of haloperidol or olanzapine appears to be appropriate.

Introduction

The occurrence of aggressive incidents in psychiatric care has a great impact on the well-being of staff and patients, and is associated with considerable costs (1-3). Considering the high impact of aggression in mental health care, prevention, and management of aggression should have high priority (4).

Several treatment approaches to manage aggressive behaviour in psychiatry exist, including psychopharmacological and behavioural approaches (5). A distinction can be made between pharmacotherapy in the acute situation versus maintenance treatment. The aim of pharmacotherapy in the two situations is different. In the acute situation, drugs are administered to stop a dangerous situation by sedation or motor interference such as muscle weakness. However, for maintenance therapy, i.e., pharmacotherapy for patients to whom aggression is an ongoing problem, long-term sedation is an undesired effect as it hampers adequate psychiatric examination, as well as the therapeutic patient relationship. Furthermore, habituation to sedatives is likely to occur. A review about the pharmacological maintenance treatment of aggressive behaviour, i.e. pharmacotherapy for patients to whom aggression is a recurrent behaviour, has been published elsewhere (6).

In this chapter we will address the pharmacotherapy of aggression in the acute situation. An overview will be given of published randomized controlled trials (RCTs) addressing the pharmacotherapy of aggression in the acute situation in general adult psychiatry. Based on this overview a guideline for pharmacotherapy in the management of aggressive behaviour in acute situations and recommendations for the conduct of future research will be proposed.

Methods

As previously stated, the aim of this chapter is to review the available evidence for the pharmacotherapy of aggression in acute situations. For this review, only published randomized controlled trials (RCTs) are considered, as these are seen as the gold standard for obtaining evidence for drug effects (7). A literature search was conducted within the PsycINFO, EMBASE, Cochrane, and PubMed databases from 1966 through March 2005 to identify published RCTs, systematic reviews, and meta-analyses assessing the efficacy of drugs for the management of aggression or aggression-related symptoms, including violence, hostility, and anger. As main search terms, we used MeSH terms, covering the words aggression, violence, anger, and hostility combined with drug therapy, psychotropic drugs, antipsychotic agents, benzodiazepines, and promethazine. Furthermore, the retrieved publications were searched for additional references.

Studies were eligible for inclusion in this review if they met the following criteria: (1) random allocation to treatment, as mentioned in the study; (2) the study population consisted of adult (aged between 18 and 65 years) general psychiatric patients in whom aggression might be an ongoing problem. Studies applying to specialized psychiatric settings—like child psychiatry, mental retardation, and organic brain diseases—or to nonpsychiatric settings—like prisons—were excluded; (3) outwardly directed aggression or aggression-related symptoms were either a primary or secondary outcome in the study; (4) the study did not address pharmacotherapy of aggression or aggression-related symptoms as maintenance treatment; (5) the study was English language and published in a peer-reviewed journal before March 2005; and (6) the study drug under investigation is currently registered by the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA). One reviewer (L.E.G.) screened abstracts to determine whether studies should be included in the review. In case of any doubt, the full paper was retrieved.

For the RCTs included, an acceptable methodological quality was required, which was defined by a Jadad score of three or more (8). The Jadad scale is an instrument to adjudicate methodological quality. Criteria used for this instrument comprise the quality of randomization, the quality of blinding, and a description of dropouts and withdrawals.

There are different theoretical concepts of aggression. Symptoms associated with aggression include hostility, agitation, violence, and anger (9-12). Because these symptoms are closely related to aggression, it is assumed that influencing them will also have an impact on any aggressive behaviour displayed. Therefore, we included all RCTs that also assessed the pharmacological management of those symptoms.

Trials assessing the pharmacotherapy for the management of acute aggression have been conducted in different psychiatric and non-psychiatric settings. Given the heterogeneity of these populations, it seems likely that study results might not be directly comparable to each other. Therefore, this review is restricted to general adult psychiatry, meaning that studies conducted in non-psychiatric setting, e.g. in prisons, and specialized psychiatric settings, i.e., organic brain diseases and mental retardation, were not included, as were studies that evaluated only children or elderly patients.

Results

From previous studies it is known that most aggressive incidents in mental health care occur during the first days of admission (13, 14). Therefore, most available trials addressing the pharmacological management of acutely aggressive patients have been conducted at acute admission wards and psychiatric emergency depart-

ments. Most trials used the "rapid tranquillization strategy" in which antipsychotics or benzodiazepines are administered in a compressed time-frame, titrating dosage against symptoms to control assaultive, hyperactive, and hostile patients (15). Ideally, the goal of this strategy is to calm down disturbed patients to such an extent that communication is possible, thereby enabling health workers to evaluate the psychiatric status. In some cases sleep can also be an appropriate goal (16, 17).

The studies evaluated are represented in Figure 1 (17-35). The study population predominantly comprised schizophrenic patients experiencing an acute exacerbation. Other diagnoses included mania and substance abuse. However, in most of the trials, substance abuse was an exclusion criterion. Another frequently established "diagnosis" was acute agitation.

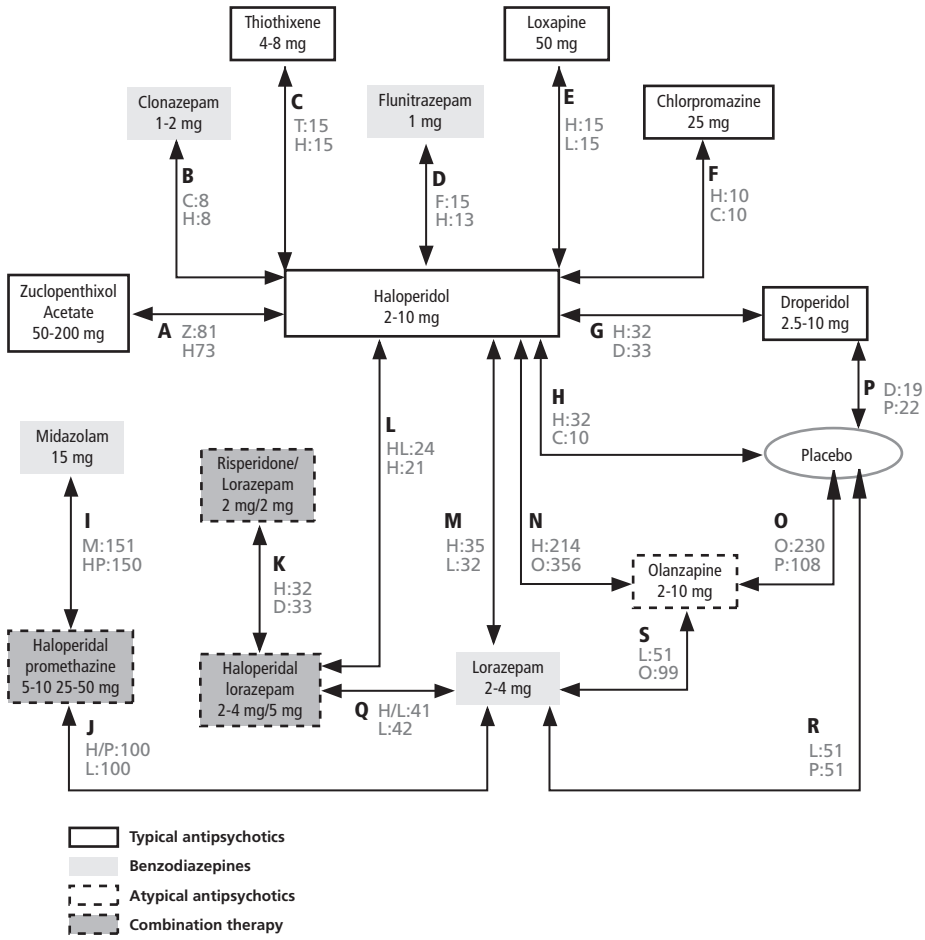
Outcome measures most frequently used to assess changes in aggressive behaviour included subscales of the BPRS (36) and the PANNS (37). Other outcome measures include sedation-scales and additional number of injections needed to calm the patient down.

Pharmacological agents used in the evaluated RCTs comprised antipsychotic agents, benzodiazepines, combination therapy of benzodiazepines and antipsychotics, and promethazine. In most studies, drugs were administered intramuscularly; one study also assessed the efficacy of oral doses (21) and one study assessed the efficacy of intravenous administration.

Typical Antipsychotics

Typical antipsychotics can be classified into high potency and low-potency antipsychotics (38). Low-potency antipsychotics, like chlorpromazine, are historically used for the management of acute agitation and aggression. However, because low-potency antipsychotics are more likely to inflict serious adverse events, e.g., excessive sedation and hypotension, compared to high-potency antipsychotics, preference is given to the latter (31, 39, 40).

Haloperidol, a high-potency antipsychotic, is the most frequently used drug in the evaluated RCTs. All formula, i.e. oral, intramuscular (IM) and intravenous (IV) have been studied. In one of the first placebo-controlled trials in this field, conducted in 1974, haloperidol in doses of 1, 2, and 5 mg was compared to chlorpromazine and placebo (31). Benefit for haloperidol in dosages of 2 and 5 mg over placebo and chlorpromazine was reported. Other typical antipsychotics investigated included droperidol, thiotixene, loxapine, and zuclopenthixol (22, 24, 27, 32). These antipsychotics were compared to haloperidol. Droperidol IV was also compared to the placebo (29). The observed differences in efficacy between the different typical antipsychotics predominantly rest on differences in pharmacokinetic properties of the different drugs. Droperidol IM induced a quicker onset of action than haloperidol as measured by the number of patients requiring an extra injection after 30 minutes (32); these results were approved by two randomized controlled trials conducted in



A = Chouinard et al., 1994; Chin et al., 1998; Taymeeyapradit and Kuasirikul, 2002; B = Chouinard et al., 1993; C = Stotsky 1977; D = Dorevitch et al., 1999; E = Fruensgaard et al., 1977; F = Reschke, 1974; G = Resnick and Burton,984; H = Reschke, 1974; Wright et al., 2001; I = TREC Collaborative Group, 2003; J = Alexander et al., 2004; K = Currier et al., 2004; L,M = Battaglia et al., 1997; N = Breier et al., 2002; Kinon et al., 2004; Wright et al., 2001; O = Meehan et al., 2001; Wright et al., 2001; P = van Leeuwen et al., 1977; Q = Bieniek et al., 1998; Battaglia et al., 1997; R,S = Meehan et al., 2001.

Figure 1 **Drugs joined by arrows have been compared to each other (in one or more studies); numbers along the arrows indicate the total number of study participants in each teeatment arm of the RCT(s). Dosages per administration are indicated under the drug name.**

emergency departments (41, 42). These studies were not included in Figure 2, because they were not conducted in a study population consisting solely of psychiatric patients. The advantage of using zuclopenthixol acetate over haloperidol was that, over a period of seven days, fewer injections were required to obtain the same effect, as zuclopenthixol acts as a short-acting depot (34). However, more extrapyramidal symptoms and sedation were reported for zuclopenthixol compared to haloperidol.

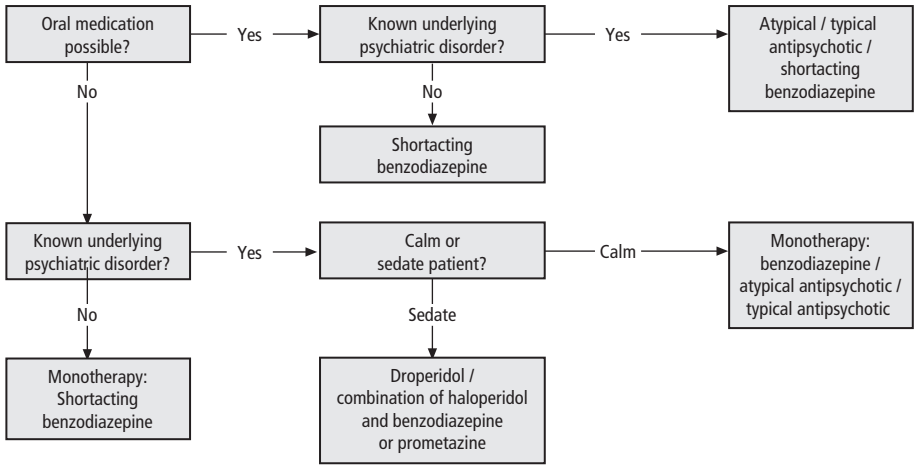


Figure 2 Proposed strategy for pharmacotherapy of aggression in an acute situation.

Benzodiazepines

Because of their anxiolytic and sedative properties and quick onset of action, benzodiazepines are extremely suitable to tranquillize aggressive patients.

The benzodiazepines studied in the RCTs comprised lorazepam (18-20, 30), flunitrazepam (23, 26). The short-acting lorazepam is the most extensively studied benzodiazepine used for the management of acute aggression. Lorazepam has been compared to haloperidol (19, 20), placebo and olanzapine (30), and combination therapy of haloperidol and promethazine (18). No significant differences between haloperidol and lorazepam were observed in the trials. However, combination therapy of haloperidol and lorazepam was superior over monotherapy of haloperidol or lorazepam in that the onset of action was more rapid (19, 20). Furthermore, heavier sedation was reached with combination therapy when compared to monotherapy. Other benzodiazepines in the evaluated studies were midazolam and clonazepam. Midazolam was found to be more rapid a sedative than the combination of haloperidol and promethazine (17). No difference in agitation scores was observed between haloperidol and clonazepam (23).

Atypical Antipsychotics

At the beginning of the 1990s risperidone, the second atypical antipsychotic in the market after clozapine, was introduced, followed by olanzapine, quetiapine, ziprasidone, and aripiprazole. Recently, intramuscular forms of the atypical antipsychotics olanzapine and ziprasidone and an oral concentrate of risperidone became available. We will not discuss ziprasidone, because in Europe at the moment this drug is only registered for use in clinical trials, due to its association with cardiac side-effects. Whereas the calming and sedating effect of typical antipsychotics is principally

mediated through dopaminergic mechanisms, the sedating and calming effect of olanzapine is likely to be mediated through histaminergic mechanisms (43, 44).

Olanzapine, after both oral and intramuscular administration, was at least as effective as haloperidol in a population of mildly agitated patients (21, 28, 35). An advantage of the use of olanzapine over haloperidol was the decreased risk of extrapyramidal symptoms in the case of olanzapine (35). Oral solution of risperidone combined with lorazepam has been compared to intramuscular administration of haloperidol and lorazepam (25). For both treatments a similar effect was reached, with more sedation observed for the intramuscular therapy between 30 minutes and 120 minutes after administration. In accordance with the Dubin, et al. study (45), in which oral administration of haloperidol and thioridazine were compared to intramuscular administration, patients randomized on oral therapy did not refuse the oral medication. In this study 30 minutes difference for time of onset was observed. These study results suggest that in certain circumstances, probably in the case of mild aggressive behaviour, oral therapy can be a good alternative to parenteral tranquillization. Intramuscular Olanzapine has also been compared to intramuscular lorazepam (30); more reduction of scores on agitation scales observed for olanzapine at 2 hours after injection.

Discussion

Limitations

Although RCTs are considered a gold standard for testing the efficacy of medical interventions (7), they also have limitations. The main methodological issues that were encountered in this review concerned the generalizability to daily clinical practice and a low statistical power for detecting differences in efficacy between the treatment groups.

Poor generalizability from clinical trial populations to patients seen in daily practice is one of the limitations particularly associated with RCTs (46). Previous studies have shown that psychiatric patients with comorbid disorders are frequently excluded from RCTs (47-49). There are indications that the aggressive patient, as seen in daily clinical practice, was excluded from the RCTs evaluated in this review.

Firstly, recruitment procedures that depend on voluntary participation (50) are likely to result in the exclusion of highly aggressive patients. Indeed, aggression at baseline was frequently low. Also, the application of strict study inclusion and exclusion criteria is likely to result in the exclusion of aggressive patients. For example, patients with substance abuse, which is associated with aggression, were frequently excluded from the RCTs we analyzed (51). Concomitant use of psychotropics was also frequently used as an exclusion criterion.

The statistical power for detecting differences between treatment groups was usually small, due to the small number of patients included in the trials, as can also

be seen in Figure 1. Besides reducing the ability to detect treatment efficacy, studies with small sample sizes will also have a limited value in detecting adverse effects. Furthermore, the baseline aggression level was frequently low. As a consequence, only a small reduction of aggressive behaviour can be achieved using pharmacotherapy and, to detect small changes, large sample sizes are required.

Advised pharmacological approach of acutely aggressive patients

Taking into account the limitations of the evaluated studies, a pharmacological treatment strategy as depicted in Figure 2 is proposed. As different studies suggest that the difference between oral and parenteral medication is not the effect reached, but the shorter time of onset when using parenteral administration, oral therapy should be considered first. If the patient is unwilling to accept oral medication, or if a shorter time of onset is desired, intramuscular medication is the therapy of choice. One should choose between the administration of antipsychotics, atypical or typical, benzodiazepines, or a combination therapy of typical antipsychotics and benzodiazepines or promethazine. The choice between these agents depends on the objective of the pharmacotherapy, i.e., very quick vs. quick response, sedative vs. calming effect, as well as the characteristics of the individual patient, for instance the underlying psychiatric disorder and the risk of adverse events.

If the underlying psychiatric disorder is unknown, the use of benzodiazepines seems to be the safest option as benzodiazepines interfere less with the diagnostic process, e.g., differentiation between substance-induced psychosis and chronic psychoses associated with chronic psychiatric disorders like schizophrenia and bipolar disorder. However, sometimes monotherapy with benzodiazepines might be insufficient. In those cases, combination therapy of benzodiazepines or promethazine with antipsychotics could be used (see also Figure 2). If the underlying psychiatric disorder is known, the following strategy is advised. If the reduction of aggressive behaviour has to be reached as soon as possible and if there are no somatic contraindications, one could opt for the administration of droperidol.

There are some concerns regarding the association between droperidol and cardiac adverse events—fatal QTc prolongations. However, reports are inconsistent. Based upon postmarketing case reports the USA's Food and Drug Administration (FDA) added a "black box" warning to the use of droperidol, which means that prescribers should consider alternative medication for patients at high risk for cardiac arrhythmias (52). In contrast, three reviews showed that there is no clear evidence about the increased risk of fatal cardiac adverse events (53-55).

A second choice of treatment, when reduction of aggressive behaviour is urgently needed, is the use of combination therapy of a typical antipsychotic and a benzodiazepine. Because haloperidol and lorazepam have been most extensively studied, we recommend the combined use of these. If the goal of therapy is of calming the patient rather than sedating or getting them to sleep, one could opt for monotherapy of an antipsychotic agent—typical or atypical—or a benzodiazepine.

The lower incidence of extrapyramidal adverse events in atypical antipsychotics compared to typical antipsychotics might favour the choice of atypical antipsychotics. However, if the choice of therapy in the acute situation determines the choice of long-term therapy, as (56) showed, the long-term side-effects associated with the use of antipsychotics should be considered; including, in the case of atypical antipsychotics, the metabolic syndrome (57), and tardive dyskinesia in the case of typical antipsychotics. Furthermore, eight cases of fatal adverse events have been reported after the use of intramuscular olanzapine in excessive dosages or in a combination with benzodiazepines and/or other antipsychotics (58).

When choosing benzodiazepines, paradoxical reactions, i.e., disinhibition, can occur (59). However, this side effect is rare. Other known side-effects include the risk of dependence, withdrawal, and tolerance, as well as respiratory arrest.

Recommendations for future research

This chapter shows that the evidence obtained by RCTs is incomplete. We found that in quite a substantial number of RCTs, statistical power was rather small. Furthermore, generalizability of study results to daily clinical practice is questionable. For future research, we recommend the conduct of large-scale pragmatic trials (49). In addition to these trials, observational study designs should be used to study the effectiveness and safety of drugs used to treat aggressive patients (48).

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Chapter 2.2

Pharmacotherapy for the treatment of aggressive behaviour in general adult psychiatry: a systematic review

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Abstract

Objective To systematically review the evidence for pharmacologic management of outwardly directed aggressive behavior in general adult psychiatry.

Methods Literature searches in PubMed, EMBASE, PsycINFO, and Cochrane libraries from 1966 through March 2005 were used to identify relevant studies. The keywords aggression, violence, anger, and hostility combined with drug therapy, psychotropic drugs, adrenergic β-antagonists, anticonvulsants, antidepressants, antipsychotic agents, benzodiazepines, and lithium were searched. Furthermore, the retrieved publications were searched for additional references.

All randomized controlled trials addressing pharmacotherapy for aggression or aggression-related symptoms were included, except studies addressing the "emergency situation" and studies conducted in specialized psychiatric or non-psychiatric settings.

Evidence synthesis was performed using the best-evidence principle. Two authors independently adjudicated methodological quality and generalizability to daily clinical practice.

Results Thirty-five randomized controlled trials met the inclusion criteria and were evaluated. On the basis of a best-evidence synthesis model, weak evidence for antiaggressive effects of antipsychotics, antidepressants, anticonvulsants, and β-adrenergic blocking drugs was found. Atypical antipsychotics appeared superior to typical antipsychotics. The use of various outcome measures and insufficient data reporting in the individual studies hampered the quantitative assessment of efficacy across studies. Further limitations of the available randomized controlled trials included small sample sizes, short study duration, and poor generalizability to daily clinical practice setting.

Conclusion Whereas pharmacotherapy is frequently applied in aggressive patients, only weak evidence of efficacy of various drug classes was found. Consensus about the use of aggression measurement scales in clinical trials is necessary for future research. Furthermore, large-scale trials with more naturalistic designs, as opposed to classical randomized controlled trials with strict inclusion and exclusion criteria, may be advisable in order to obtain results that are more generalizable to daily clinical practice.

Introduction

In mental health care, aggression is an important issue, with, for example, an incidence of 9.3 incidents per bed per year in Europe at acute admission wards (1). Besides high costs (2), aggression influences therapeutic environment and well-being of both patients and staff workers (3,4). In a recent study conducted in East London, more than 1 out of every 5 psychiatric nurses reported that they had not been able to go to work owing to workplace violence during the preceding year (5). Although far less investigated, aggression also appears to be a common phenomenon in psychiatric outpatients (6)

Given the incidence and impact of aggression, management of aggression has high priority in mental health care. Most aggressive incidents occur during the first week following admission (7). In a small proportion of patients, aggression will remain an ongoing problem (8–10).

Several interventions are used to manage aggressive behavior, including cognitive therapy and training of nursing staff in the case of hospitalized patients (11–13). Pharmacotherapy is also frequently used in aggressive patients (14). Several drugs, including anticonvulsants, antipsychotics, and antidepressants, have been used for repetitively aggressive patients (11,12). A small number of systematic reviews have evaluated the evidence for the use of these drugs (15–17). However, the most recent reviews investigating the evidence for efficacy of pharmacotherapy for the ongoing management of aggression in psychiatric patients date from 1996 and 1997 (15,16). In these reviews, clinical trials as well as case reports were included. To our knowledge, a systematic review on this subject based upon randomized controlled trials (RCTs)- considered as the gold standard to obtain evidence (18) -never has been conducted. The objective of this review is to systematically review the literature for the evidence of the pharmacologic management of aggression in repetitively aggressive patients in general adult psychiatry, restricting ourselves to RCTs. Randomized controlled trials have some limitations as well, e.g., strict inclusion and exclusion criteria, which are likely to reduce the generalizability to daily clinical practice (19); we also intended to assess the generalizability of the evidence.

Methods

Data sources

A literature search was conducted within the PsycINFO, EMBASE, Cochrane, and PubMed databases from 1966 through March 2005 to identify published RCTs, systematic reviews, and meta-analyses assessing the efficacy of drugs for the management of aggression or aggression-related symptoms, including violence, hostility, and anger. As main search terms, we used MeSH terms, covering the words

aggression, violence, anger, and hostility combined with drug therapy, psychotropic drugs, adrenergic β-antagonists, anticonvulsants, antidepressants, antipsychotic agents, benzodiazepines, and lithium. Furthermore, the retrieved publications were searched for additional references.

Study selection

Studies were eligible for inclusion in this review if they met the following criteria: (1) random allocation to treatment, as mentioned in the study; (2) the study population consisted of adult (aged between 18 and 65 years) general psychiatric patients in whom aggression might be an ongoing problem. Studies applying to specialized psychiatric settings -like child psychiatry, mental retardation, and organic brain diseases- or to nonpsychiatric settings -like prisons- were excluded; (3) outwardly directed aggression or aggression-related symptoms were either a primary or secondary outcome in the study; (4) the study did not address pharmacotherapy of aggression or aggression-related symptoms in the emergency situation; (5) a previously published scale was used to measure aggression or aggression-related symptoms; (6) the study was English language and published in a peer-reviewed journal before March 2005; and (7) the study drug under investigation is currently registered by the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA). One reviewer (L.E.G.) screened abstracts to determine whether studies should be included in the review. In case of any doubt, the full paper was retrieved. If there was still any doubt, the study was judged by a second reviewer (E.R.H. or J.J.S.).

Data extraction

Trials were categorized into subgroups according to therapeutic drug class. For every subgroup, evidence of efficacy was determined. Because effect sizes were difficult to compute owing to the use of a variety of continuous outcome scales, evidence of efficacy was determined using the best-evidence synthesis principle (20). The best-evidence synthesis method used in this review is based on the model of van der Windt et al. (21) In this model, studies are weighted according to methodological quality, clinical relevance, and statistical significance. Distinction was made between insufficient, weak, and strong evidence of efficacy or evidence of no efficacy, using decision rules presented in Figure 1 (22).

Using this method, at least 3 studies assessing the drug are required to obtain weak or strong evidence of efficacy.

Quality assessment

The Jadad scale (scores range from 0 to 5) was used to adjudicate the methodological quality of the studies (23). Two reviewers performed this assessment independently (L.E.G. and E.R.H. or J.J.S. or T.C.G.E.). Interrater agreement was

calculated using the kappa statistic. Subsequently, disagreement was discussed and resolved. Studies with Jadad scores of 3 or more were rated as having an acceptable methodological quality.

Quantitative data synthesis

Effect sizes were expressed as standardized mean difference (SMD) (24). The SMD was interpreted as described by Cohen (25) and applied using the following effect sizes: small 0.2, medium 0.5, and large 0.8. The SMD can only be applied to normally distributed data. In case of skewed data, the SMD cannot be computed. We investigated skewness by dividing mean through standard deviation; a value of less than twice the standard deviation was indicative of skewed data (26).

Study generalizability

To our knowledge, no validated checklists or methods to rate generalizability to daily clinical practice are available. Therefore, we defined our own criteria. Generalizability was defined as the probability that aggressive patients as seen in daily clinical practice would be included in the study. Generalizability was scored on a scale from 1 to 5, where studies with a score of 3 or more were considered to have an acceptable generalizability. To generate this score, the following 2 items were considered: (1) The source population is representative for psychiatric patients seen in daily clinical practice and (2) No inclusion or exclusion criteria that could exclude typical aggressive psychiatric patients, e.g., a history of drug abuse, violence in the past, or the use of concurrent psychotropics, were applied.

The same 2 independent reviewers who assessed the Jadad scores also assessed the generalizability. Interrater agreement was calculated using the kappa statistic. Subsequently, disagreement was discussed and resolved.

Results

Study selection

As can be seen in Figure 2, the use of our search terms resulted in the identification of 467 publications. On the basis of the title and the study abstracts, 425 studies were excluded from further analysis; the remaining 42 full papers were retrieved and screened. Reasons for exclusion are shown in Figure 2. Finally, we located 35 RCTs (27–61) describing the effect of different drugs on aggression or aggression-related symptoms.

Study characteristics

Detailed study characteristics are summarized in Table 1. The study outcomes are displayed in Table 2.

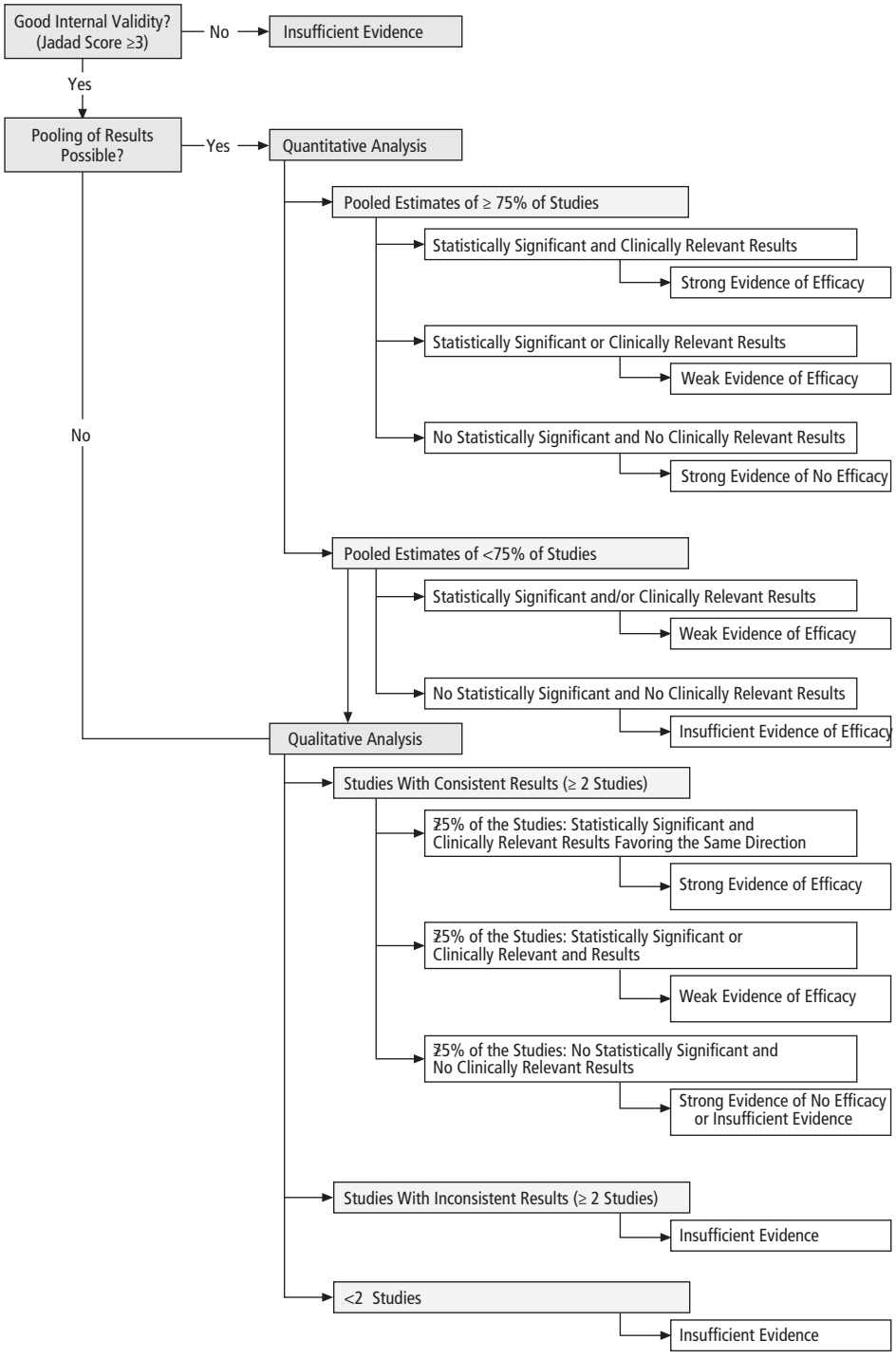
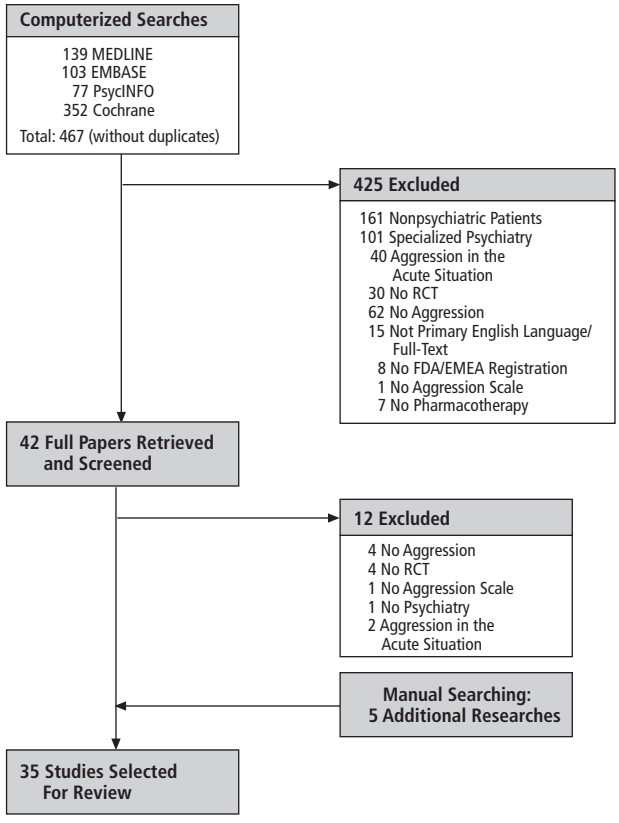


Figure 1 Beste-evidence synthesis adapted with permission from Smidt et al.[22]



Abbreviations:
EMEA = European Agency for the Evaluation of Medical Products;
FDA = U.S. Fool and Drug Administration;
RCT = Randomized Controlled Trial.

Figure 2 Study selection.

Outcome measures

A whole range of different outcome measures -21 in total- were used in the RCTs included and involved observational scales as well as self-report scales. Furthermore, some scales were especially designed for measuring aggression, while others were subscales measuring items related to aggression in a broader perspective, for example the anger scale of the Profile of Mood States (79)

The most frequently used specific aggression scales were different versions of the Overt Aggression Scale (OAS) (62) From the 21 used outcome scales, the OAS modified for outpatients was used more often. Other outcome measures included diagnosis-related scales, like subscales of the Positive and Negative Syndrome Scale

(PANSS) (63) and the Borderline Personality Disorder Severity Index (BPDSI) (64).

Patients

Most studies were conducted in a schizophrenic population[i] or cluster B personality disordered patients.[ii] The other diagnoses included posttraumatic stress disorder (PTSD) (35,45,58), autistic disorder (44) intermittent explosive disorder (43) attention-deficit/hyperactivity disorder (29) anorexia nervosa (38) and depressive disorder (36,39,41). Of the 35 studies, 15 were conducted in a population solely consisting of outpatients.[iii]

Follow-up

The follow-up period ranged from 3 to 24 weeks. In the majority of studies,[iv] the follow-up period was 6 to 12 weeks, while 7 studies[v] had a long-term follow-up (>12weeks) and 9 studies[vi] had a short-term follow-up (<6 weeks).

Control group

Of the 35 RCTs, 27 compared active drug(s) to placebo. The other studies[vii] used an active drug as control.

Of the 35 RCTs included in this review, 33 were double blind and 2 were not (38,43). In 3 studies (29,32,52), a crossover design was used. In one study (43), the outcome measurement was assessed single blind.

Quality assessment

In 31 of the 35 RCTs, the methodological quality was judged acceptable as reflected by a score on the Jadad list of 3 or more. The 4 studies with a Jadad score of less than 3 (28,38,39,43) were excluded from the evidence synthesis. Interrater agreement for the Jadad score was good (kappa statistic=0.73).

Generalizability

Generalizability to daily clinical practice was judged to be acceptable for 20 of the 35 studies (Table 2). Several factors contributed to poor generalizability.

In most studies, eligibility criteria did not comprise a certain baseline level of aggression before the start of the trial, as measured by a scale. This might have con-

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i References 27, 28, 30–34, 42, 47, 52, 59–61

ii References 37, 40, 46, 48–51, 53–57

iii References 35, 38–41, 45, 46, 48, 49, 53–58

iv References 27, 28, 32, 35, 38, 39, 41, 42, 44–46, 48, 54–57, 60, 61

v References 29, 34, 40, 47, 49, 52, 53

vi References 30, 31, 33, 36, 37, 50, 51, 58, 59

vii References 27, 29, 34, 36, 43, 54, 59, 60

tributed to a low baseline level of aggression in some of the studies. Furthermore, current drug abuse, alcohol abuse, or other psychotropic medication use, factors associated with aggression (14,84) were frequently used as exclusion criteria.[viii]

Furthermore, in many studies, the recruitment method did not favor inclusion of patients for whom aggression appears to be an ongoing problem: in some studies, patients were recruited through advertisement (40,48,49,53–55). As aggressive patients are less likely to give informed consent, this method might lead to "volunteer bias" (85). In other studies, the source population comprised patients with an acute exacerbation of schizophrenia (30,31,33,42,59). Acute exacerbation is associated with aggression, especially in the first week of admission; however, once the patient is stabilized, aggression will probably not remain as an ongoing problem (8). Inter-rater agreement for the generalizability was good (kappa statistic=0.60).

Evidence synthesis for the different drug classes

Evidence of efficacy for the different drug classes, i.e., antipsychotics, antidepressants, anticonvulsants, and β-adrenergic blockers, is displayed in Table 3.

We were not able to calculate the SMD for most of the studies because many studies did not provide the required data. In those studies for which the required data were provided, the distribution appeared skewed (26). In the latter studies, the SMD can be calculated from log-transformed data, which were not available directly from the studies. Consequently, we could only perform a qualitative evidence synthesis.

Antipsychotic agents

Two 3-armed RCTs (50,51) performed by the same research group in a borderline personality disordered population comparing haloperidol and an antidepressant to placebo were found. In both studies (50,51), haloperidol was found to be statistically significantly superior to placebo on the Hopkins Symptom Checklist-90 (SCL-90) (74) but not on the Inpatient Multidimensional Psychiatric Scale (IMPS) (75) hostility items. In one 3-armed RCT (61) comparing risperidone to haloperidol and placebo in a schizophrenic population, no benefit for haloperidol as compared to placebo was found.

Seven studies with acceptable methodological quality comparing atypical antipsychotics to haloperidol and/or placebo in subjects with schizophrenia (27,34,59–61), borderline personality disorder (53) or posttraumatic stress disorder (45) were evaluated. In 2 large-scale studies, risperidone was superior to haloperidol (60,61) and placebo (61) on the PANSS hostility factor in dosages of more than 2 mg daily. In 4 studies (27,34,45,59) comparing risperidone to haloperidol

viii References 29, 35, 37, 39–42, 44, 46, 48–50, 53–58

Table 1 Study characteristics

Study	Diagnosis	Aggression before trial[a]
Antipsychotic agents		
Blin[59] 1996	Schizophrenia, acute exacerbation with symptoms of anxiety, inpatients	NAR
Citrome et al[34] 2001	Schizophrenia or schizoaffective disorder: treatment -resistant to previous neuroleptics, inpatients	NAR
Czobor et al[28] 1995	Schizophrenia, inpatients	PANSS hostility > 2
Marder et al[61] 1997	Schizophrenia, inpatients	NAR
Min et al[27] 1993	Schizophrenia, inpatients	NAR
Monnelly et al[45] 2003	Combat related PTSD, outpatients	NAR
Peuskens[60] 1995	Schizophrenia, inpatients	NAR
Zanarini & Frankenburg[53] 2001	Borderline personality disorder, outpatients	NAR
Beta-adrenergic blocking drugs		
Allan et al[30] 1996	Schizophrenia, male, inpatients	NAR
Alpert et al[31] 1990	Schizophrenia, schizoaffective disorder, bipolar disorder, male, inpatients	NAR
Caspi et al[32] 2001	Schizophrenia, male, inpatients	≥ 4 incidents in 1 month
Maoz et al[42] 2000	Schizophrenia and schizofreniform disease, acute exacerbation, inpatients	NAR
Ratey et al[47] 1992	Schizophrenia, schizoaffective disorder, mentally retarded, inpatients	NAR
Anticonvulsants		
Citrome et al[33] 2004	Schizophrenia, inpatients	≥ 6 points on PANSS subscale
De la Fuente and Lotstra[37] 1994	Borderline personality disorder, inpatients	NAR
Frankenburg and Zanarini al[40] 2002	Borderline personality disorder with a comorbid bipolar II disorder outpatients, women	NAR
Hollander et al[56] 2003	Cluster B personality disorder, outpatients	≥ 15 point on OAS-M
Hollander et al[55] 2001	Borderline personality disorder, outpatients	NAR
Nickel et al[46] 2005	Borderline personality disorder, male outpatients	NAR

Exclusion criteria	Weeks[b]	Drugs	: N, N[c]
Relevant somatic disorder, history of drug or alcohol abuse during past year, schizo-affect. disorder, long-acting antipsychotics	4	Haloperidol Risperidone Methotrimeprazine	: 20, 14 : 21, 17 : 21, 14
History of treatment-resistancy to study drugs	14	Clozapine Risperidone Olanzapine Haloperidol	: 40, 32 : 41, 28 : 39, 30 : 37, 25
Comorbid psychiatric disorder, drug or alcohol abuse in the past 6 months, relevant somatic disorder	8	Risperidone Haloperidol Placebo	: 85, ? : 24, ? : 30, ?
Comorbid psychiatric disorder, drug or alcohol abuse in the past 6 months, relevant somatic disorder	8	Risperidone Haloperidol Placebo	: 342, 193 : 85, 35 : 86, 27
Relevant somatic disorder, drug or alcohol abuse during past year, comorbid psychiatric disorder	8	Risperidone Haloperidol	: 16, 13 : 19
History of antipsychotic use, schizophrenia, bipolar disorder, organic mental disorder	6	Risperidone Placebo	: 8, 7 : 8, 8
Comorbid psychiatric disorder, relevant somatic disorder, history of alcohol or drug abuse in previous 12 months,	8	Risperidone Haloperidol	: 1136, 856 : 226, 205
Relevant somatic disorder, current drug or alcohol abuse, use of psychotropics	24	Olanzapine Placebo	: 10, 8 : 9, 4
Relevant somatic disorder	3	Nadolol Placebo	: 16 : 17, 166
Relevant somatic disorder	3	Nadolol Placebo	: 16, 15 : 16, 16
Relevant somatic disorder	6	Pindolol/Placebo crossover	: 30, 23
Physical disorder, current drug abuse, depot neurolepticum	8	Propranolol Placebo	: 18, 18 : 16, 16
Relevant somatic disorder	13	Nadolol Placebo	: 22, 16 : 26, 25
Schizoaffective disorder, mood disorder, current serious violent ideas, relevant somatic disorder	4	Divalproex sodium Placebo	: 125, 120 : 124, 122
DSM-IIIR Axis 1 disorder, somatic disorder, suspected poor treatment compliance, inability to stop drug or alcohol use.	4,5	Carbamazepine Placebo	: 10, 8 : 10, 10
Relevant somatic disorder, current drug abuse		Divalproex sodium Placebo	: 20, 20 : 10, 10
Psychotic disorder, mood disorder, current drug abuse, relevant somatic disorder	12	Divalproex sodium Placebo	: 43, 39 : 48, 46
Psychotic disorder, mood disorder, relevant somatic disorder, no other psychotropics (except antidepressants)	10	Divalproex sodium Placebo	: 12, 6 : 4, 0
Schizophrenia, major depression/bipolar disorder, other psychotropics, substance abuse	8	Toparimate Placebo	: 22, 22 : 22, 20

Table 1 Study characteristics (cont.)

Study	Diagnosis	Aggression before trial[a]
Antidepressants		
Coccaro & Kavoussi[57] 1997	Personality disorder, outpatients	≥ 15 points OAS-M for 1 month
Davidson et al[36] 1981	Depressed inpatients	NAR
Davidson et al[35] 2002	PTSD, outpatients	NAR
Mc Dougle et al[44] 1996	Autistic disorder, in- and outpatients	NAR
Fava et al[39] 1997	Depressed outpatients	NAR
Fassino et al[38] 2002	Anorexia nervosa, outpatients	NAR
van der Kolk et al[58] 1994	PTSD outpatients	NAR
Rinne et al[48] 2002	Borderline personality disorder, outpatients	NAR
Salzman et al[49] 1995	Borderline personality disorder, outpatients	NAR
Vartiainen et al[52] 1995	Schizophrenia, inpatients	≥ 1 incident/ month on SOAS for 2 months
Others[d]		
Dorrego et al[29] 2002	ADHD, inpatients	NAR
Lipman et al[41] 1986	Depressive and anxiety disorder, outpatients	NAR
Mattes[43] 1990	Intermittent explosive disorder , inpatients	NAR
Soloff et al[51] 1989	Borderline personality disorder, inpatients	NAR
Soloff et al[50] 1993	Borderline personality disorder, inpatients; follow-up partly after admission	NAR
Zanarini et al[54] 2004	Borderline personality disorder, female outpatients	NAR

[a] Aggression before trial: minimal required frequency and/or severity for study inclusion.
[b] Duration of the trial treatment phase.
[c] First number represents the number of participants at the beginning of the study; second number indicates the number of participants minus dropouts.
[d] The Others category represents studies comparing active drugs of two different classes.

Exclusion criteria	Weeks[b]	Drugs	: N,N[c]
Schizophrenia, mood disorder, delusional disorder, currently drug or alcohol dependent	12	Fluoxetine Placebo	: 27, 14 : 13, 9
Psychotic disorder, mania, mental retardation, organic brain syndrome	3	Phenelzine Imipramine	: 24, 21 : 25, 22
Psychotic disorder, bipolar disorder, major depression, anxiety disorder, organic mental disorder, alcohol or drug dependence/use, relevant somatic disorder, other psychotropics, cognitive behavioral therapy	12	Sertraline Placebo	: 194, 191 : 201, 194
Illicit substance abuse, notable medical condition, other psychotropics, psychotic disorder	12	Fluvoxamine Placebo	: 15, 15 : 15, 15
Pregnancy, unstable medical illness, drug abuse, psychotic disorder, bipolar disorder, pregnancy	12	Sertraline Imipramine Placebo	: 17 , ? : 21, ? : 19, ?
Psychiatric comorbidity	12	Citalopram Placebo	: 26, 19 : 26, 20
Schizophrenia, bipolar disorder, drug or alcohol addiction, organic mental disorder	5	Fluoxetine Placebo	: 33, 21 : 31, 27
No other psychotropics during the trial	6	Fluvoxamine Placebo	: 20, 16 : 18, 14
History of hospitalization, drug or alcohol abuse, recent suicidal behavior, self mutilation, use of other psychotropics	13	Fluoxetine Placebo	: 13, ? : 9, ?
Depression, relevant somatic disorder	24	Citalopram/ placebo crossover	: 19, 14
Substance abuse, IQ<75, neurological disorder, pregnancy	18	Lithium/ Methylphenidate crossover	: 32, 23
Drug/alcohol addiction, mental retardation, psychosis, bipolar disorder	8	Imipramine Clordiazepoxide Placebo	: 149, 103 : 140, 95 : 136, 87
Diagnoses requiring other treatment	Unclear	Carbamazepine Propranolol	: ?, 22 : ?, 29
Schizoaffective disorder, schizophrenia, mania, hypomania	5	Haloperidol Amitriptyline Placebo	: 31, 28 : 30, 29 : 29, 28
Drug or alcohol dependence, seizures, mental retardation,	5	Haloperidol Phenelzine Placebo	: 36, 30 : 38, 34 : 34, 28
Active drug or alcohol abuse, psychotropic use, suicidal, medically ill, seizures, depression	8	Olanzapine Fluoxetine Ol/Fl	: 16, 16 : 14, 13 : 15, 13

Abbrevations: NAR= No aggression baseline required (for study-inclusion) OAS-M = Overt Aggresion Scale-Modified, PANSS = Positive and Negative Syndrome Scale, PTSD = posttraumatic stress disorder, Symbol: ? = number not stated.

Table 2 Study Outcomes

Study	Measures	Side effects
Antipsychotic agents		
Blin et al[59] 1996	PAS	No serious side effects. More extrapyrimidal symptoms in haloperidol group, except hypokinesia and bradykinesia, which were higher for risperidone group
Citrome et al[34] 2001	PANSS hostility	7 patients with hematological problems and seizures (unclear which arm)
Czobor et al[28] 1995	PANSS hostility	Not mentioned
Marder et al[61] 1997	PANSS hostility-excitement	Not mentioned
Min et al[27] 1993	PANSS hostility	No between-group differences; no serious side effects.
Monnelly et al[45] 2003	OAS-M STAS-S, STAS-T and BDHI	Mild side effects in both groups
Peuskens[60] 1995	PANSS hostility	More extrapyrimidal symptoms for haloperidol; increase of weight for risperidone
Zanarini & Frankenburg[53] 2001	SCL-90	In the olanzapine group 1 patient with EPS and in the whole group weight-gain
Beta-adrenergic blocking drugs		
Allan et al[30] 1996	BPRS hostility factor	1 dropout in both groups due to blood pressure drops
Alpert et al[31] 1990	OAS	1 dropout in both groups due to blood pressure drops
Caspi et al[32] 2001	OAS	3 dropouts due to adverse events: bronchitis/ syncope/ bronchospasm/ behavioral detoriation
Maoz et al42 2000	OAS, CGI-S, STPI-anger state, STPI anger-trait, MAI	Less EPS in the propranolol group
Ratey et al47 1992	OAS BPRS hostility-suspicion	4 dropouts due to adverse events: low blood pressure/ syncope/ bronchospasm
Anticonvulsants		
Citrome et al[33] 2001	PANSS hostility	No serious side effects; no between- group differences
De la Fuente and Lotstra[37] 1994	SCL-90	Not mentioned
Frankenburg and Zanarini[40] 2002	SCL-90 hostility/anger ; OAS (McLean version)	Low rate of adverse events in both groups
Hollander et al[56] 2003	OAS- (Modified for outpatients)	Mild to moderate in severity; 21(active drug) vs. 4 (placebo) dropouts due to adverse events
Hollander et al[55] 2001	OAS-M, AQ	Not mentioned
Nickel et al[46] 2005	Staxi (5 different anger subscales)	Weight reduction; no severe adverse effects.

Jadad Score[a]	Generalizability[b]	Outcome[c]
3	1	NS
4	1	Clozapine SS to risperidone and haloperidol, but not to olanzapine. Improvement for clozapine, but not for other drugs was independent from overall antipsychotic effect.
2	1	Risperidone SS superior to haloperidol and placebo Haloperidol not SS as compared to placebo
3	1	Risperidone SS superior to haloperidol and placebo
4	1	NS
3	0	NS
4	1	SS
5	0	SS
3	1	NS
3	1	Not presented
3	1	SS (frequency and severity)
4	0	SS for STPI anger stait and trait, not for other outcomes
4	1	SS for OAS
3	1	SS better results at day 3 + 7; but not at endpoint
3	0	NS
5	0	SS on both scales
3	1	SS
3	0	NS improvement
3	0	SS improvement on 4 of the 5 sub-scales

Table 2 Study Outcomes (cont.)

Study	Measures	Side effects
Antidepressants		
Coccaro & Kavoussi[57] 1997	OAS-M AQ, CGI-I	Mild-moderate; 1 dropout due to adverse events
Davidson et al[36] 1981	SCL-90 anger scale	Not mentioned
Davidson et al[35] 2002	Davidson Trauma Scale; anger irritability subscale	Not mentioned
Mc Dougle et al[44] 1996	Brown aggression scale78	No medical significant side effects.
Fava et al[39] 1997	AAQ	Not mentioned
Fassino et al[38] 2002	STAXI anger scale	Not mentioned
van der Kolk et al[58] 1994	Buss-Durkee	Diarrhea, sweating and headaches more frequently in fluoxetine group
Rinne et al[48] 2002	BPDSI: anger subscale	More nausea in fluvoxamine group.
Salzman et al[49] 1995	POMS, OAS (McLean version)	Not mentioned
Vartiainen et al[52] 1995	SDAS CGI-SI, SOAS	No significant differences between active drug and placebo
Others[d]		
Dorrego et al[29] 2002 Crossover	OAS	MPH: nausea, weight loss Lithium: motor slowness
Lipman et al[41] 1986	HSCL-80	Clordiazepoxide: drowsiness Imipramine: higher pulse rate and blood pressure
Mattes[43] 1989	Global improvement rating scale	Not mentioned
Soloff et al[51] 1989	Buss-Durkee; SCL-90; IMPS hostile belligerence	Not mentioned
Soloff et al[50] 1993	Buss-Durkee; SCL-90; IMPS hostility	Not mentioned
Zanarini et al[54] 2004	OAS-M	More sedation and weight gain in the Olanzapine monotherapy group.

[a] **Jadad-score: ≥3= acceptable methodological quality.**
[b] **0= poor generalizability; 1= acceptable generalizability.**
[c] **SS: Statistically significant in favor of the active drug compared to placebo unless specified otherwise; NS=Not significant.**
[d] **The Others category represents studies comparing active drugs of two different classes.**

Abbreviations for outcome measures and associated references: AAQ = Anger Attacks °Questionnaire74; AQ = Aggression Questionnaire75; Buss-Durkee = Buss-Durkee Hostility Inventory76; BPDSI = Borderline Personality Disorder Severity Index64

or placebo, no benefit for risperidone was reported. However, in 3 of these studies (27,45,59) sample size was small, and in one study only a 0.5-mg daily dose of risperidone was used (45). One study (34) showed clozapine to be significantly

Jadad Score[a]	Generalizability[b]	Outcome[c]
3	1	SS from week 10 till endpoint
5	0	Imipramine SS to phenelzine
4	0	SS
4	1	SS from week 4 till endpoint
2	1	NS
2	0	SS
3	1	NS
3	0	NS
4	0	POMS: SS OAS-R: NS
3	1	SS: frequency SOAS
4	1	Same effect in both arms.
4	0	No improvement from baseline for I on HSCL anger-hostility; for C detoriation from baseline
2	1	No difference between C and P
4	1	Haloperidol SS improvement compared to amitriptyline and placebo Amitriptyline SS only on BDHI compared to Placebo
3	0	Haloperidol SS improvement compared to phenelzine and placebo on the IMPS (not on other scales)
3	0	Olanzapine as efficacious as OFC in reducing aggression

BPRS = Brief Psychiatric Rating Scale77; CGI-S/I = Clinical Global Impression: aggression Severity/ Improvement79; DTS = Davidsson Trauma Scale80; SCL = Hopkins Symptom Checklist; hostility/ anger items81

IMPS = Inpatient Multidimensional Psychiatric Rating Scale82; MAI = Multidimensional Anger Inventory83; OAS= Overt Aggression Scale (modified for outpatients) 62, 843refs in JCP; PANSS = Positive And Negative Syndrome Scale63; PAS = Psychotic Anxiety Scale85

POMS = Profile of Mood States86; SDAS = Social Dysfunction and Aggression Scale73; SOAS = Staff Observation Aggression Scale72; STAS-S = Spielberger State-Trait Anger Scale-State version, ref; STAS-T = Spielberger State-Trait Anger Scale-Trait version, ref; STAXI = Stait Trait Anger Expression Inventory87; STPI = Stait-Trait Personality Inventory88

superior to haloperidol, risperidone, and olanzapine in reducing hostility apart from the overall antipsychotic effect in a schizophrenic population resistant to previous neuroleptic treatment. The antiaggressive mechanism of clozapine in that study

appeared unrelated to overall psychopathological improvement. One study (53) showed olanzapine to be superior to placebo in borderline personality disordered outpatients.

Overall, we conclude that there is weak evidence of efficacy for antipsychotic agents in treatment of aggression. Furthermore, weak evidence was found for the superiority of atypical antipsychotics over typical antipsychotics.

β-*Adrenergic blockers*

β-Adrenergic blockers are effective in decreasing aggression in organic brain diseases (86). For the general adult psychiatric population, we found 5 studies (30–32,42,47), all conducted in a schizophrenic population. In 3 studies using the β-adrenergic blocker pindolol, propanolol, or nadolol and conducted in a chronic schizophrenic population, a significant reduction of aggression was found with β-adrenergic blockers as compared to placebo. Two (32,47) of these 3 studies were conducted in a chronic schizophrenia population. The 2 studies (30,31) not showing positive results in favor of the β-blockers were conducted in a population consisting of schizophrenic patients with an acute exacerbation. Thus, according to our decision rules, there is weak evidence for the antiaggressive properties of β-adrenergic blocking drugs in schizophrenic patients. However, it is unclear whether these benefits outweigh the observed adverse events like syncopes and bronchospasms.

Anticonvulsants

Four studies were retrieved assessing antiaggressive properties of valproate (divalproex sodium), compared to placebo (33,40,55,56). Furthermore, in one study, topiramate was used as active drug (46) and, in another study, carbamazepine was used (37) In 3 of the 6 studies (40,46,56) anticonvulsants were superior to placebo. The patient populations in these 3 studies consisted of cluster B personality disordered outpatients. In the 3 studies not favoring anticonvulsants over placebo, either the sample size was low (37,55) or the population consisted of patients with an acute exacerbation of mental illness (33), which suggests that the statistical power was low.

With 3 of the 6 studies favoring anticonvulsants to placebo, we concluded that there is weak evidence of efficacy in the management of aggression with anticonvulsants in cluster B personality disordered outpatients. No serious adverse events were observed or mentioned in the different studies.

Antidepressants

Ten studies with acceptable methodological quality comparing antidepressants to placebo were evaluated (35,41,44,48–52,57,58). Of the 10 available studies, 6 studies (fluoxetine (57) fluvoxamine (44) sertraline (35), amitriptyline (51), imipramine (36), and citalopram (52) with clinical heterogeneity across studies (autism (44) PTSD (35) schizophrenia (52) depression (36) and cluster B personality disorder

Table 3 Evidence synthesis

	Qualitative evidence synthesis				
Drug	**N**	**k**	**SS**	**Obtained evidence**	**Acceptable Generalizability**
Classical antipsychotics vs placebo	308	3	2/3	Weak evidence of efficacy	2/3
Atypical antipsychotics vs placebo and/ or haloperidol	2122	7	3/7	Weak evidence of efficacy compared to placebo and haloperidol	5/7
Beta-adrenergic blockers vs placebo	169	5	3/5	Weak evidence of efficacy	4/5
Anticonvulsants vs placebo	450	6	3/6	Weak evidence of efficacy	2/6
Antidepressants vs placebo	1024	10	6/10	Weak evidence of efficacy	6/10

N= Total number of study-participants; k= number of studies; SS= Statistically Significant

(51,57)) showed a significant improvement for the active drug group compared to the placebo group. The total study follow-up of 4 of 6 studies with positive results was 12 or 13 weeks (35,44,52,57), while, in 4 studies not favoring antidepressant to placebo (41,48,50,58) the study duration was less than 12 weeks (a range from 5 to 8 weeks). Additionally, in 2 of 6 studies with positive results (52,57), patients were required to have a certain baseline level of aggression compared to none of the 5 studies not showing positive results. Furthermore, in 1 study (36) comparing imipramine to phenelzine, superiority of imipramine was observed. We conclude that there is weak evidence of efficacy for the use of antidepressants for the management of aggression across a diversity of diagnoses.

Comparison of different drug classes

We found 4 studies (29,41,43,54) that could not be classified into subgroups because drugs belonging to 2 different therapeutic drug classes were compared to each other (carbamazepine vs propranolol (43) lithium vs methylphenidate (29) the combination of olanzapine and fluoxetine vs monotherapy (54) and imipramine vs chlordiazepoxide (41). One of those studies (43) which compared carbamazepine to propranolol, had poor internal validity as reflected by a Jadad score of less than 3 and, therefore, was not evaluated for evidence synthesis. In the other 3 studies (29,41,54) efficacy is suggested for both the combination therapy of olanzapine and fluoxetine and monotherapy of olanzapine compared to monotherapy of fluoxetine (54) and imipramine compared to chlordiazepoxide (41) and no differences between lithium and methylphenidate were observed.

Discussion

Although aggressive patients use more psychotropics as compared to nonaggressive patients, no strong evidence of efficacy was found for any of the drug classes. Weak evidence of efficacy was found for antipsychotics, antidepressants, anticonvulsants, and β-adrenergic blocking drugs. Atypical antipsychotics were found to be superior to typical antipsychotic agents. Several methodological and generalizability issues complicated the evidence synthesis.

Methodological limitations

In most studies evaluated, the follow-up period was 6 to 12 weeks, but 9 studies had less than 6 weeks of follow-up.

Although 3 to 6-week trials can, in some cases, be considered adequate, for instance in the case of antipsychotics (87), longer follow-up seems more appropriate when studying the effects of the treatment of aggression. Firstly, longer follow-up might be required to reach optimal drug efficacy, and, secondly, changes in aggressive behavior are usually measured more reliably in a longer followup period when incident-based instruments or self-report questionnaires are used to measure changes in aggressive behavior. Incident-based measurement scales, like the OAS (62) and the Staff Observation Aggression Scale (SOAS) (65), are designed to detect changes in aggressive behavior by measuring the frequency and the severity of observed aggressive incidents. Especially when the baseline frequency of aggressive behavior is low, longer follow-up is required to be able to detect changes in aggressive behavior reliably. In addition, when self-report questionnaires are used to measure changes in aggressive behavior, a potential lag time between the patients' self-recognition that aggressive behavior has diminished in frequency and severity and self-perception that one is still capable of engaging in aggressive acts warrants a longer prospective window of patient assessment (57).

Different limitations influenced the statistical power of the studies. When study power is low, insufficient evidence of efficacy does not automatically implicate evidence of no efficacy. We identified the following 4 factors that may have led to a lack of power in individual studies to show evidence of efficacy of one drug above another. Firstly, study samples tended to be small. Secondly, because we expected few trials to investigate drug effects as primary outcome, we also included RCTs investigating drug effects on aggression or aggression-related symptoms as a secondary outcome. However, as the studies with aggression or aggression-related symptoms as a secondary outcome are not primarily designed to detect reduction in aggressive behavior, they might lack power to show evidence of efficacy. The third factor that might have led to a reduction of statistical power was the low baseline aggression in several studies. The use of a minimum baseline aggression level as an inclusion criterion can avoid this problem. A fourth factor that might have

lowered the statistical power is the use of an inadequate source population. In some of the studies, the study population consisted of schizophrenic patients experiencing an acute exacerbation (30,31,33,42). Acute psychiatric illness is associated with aggression; however, once stabilized, aggression does not necessarily remain an ongoing problem. To avert the problem of low statistical power, we intended to meta-analyze the study results. For meta-analysis, calculation of effect sizes is required. As numerous continuous scales were used in the individual studies, study outcomes were not directly comparable. In such cases, the computation of standardized effect sizes, i.e., SMD, is required. Unfortunately, either many studies did not provide the data required to calculate this effect size, or the reliability of such data was considered doubtful. We, therefore, had to rely on qualitative evidence synthesis instead of quantitative data synthesis.

The impossibility of calculating effect sizes not only precluded quantitative evidence synthesis, but also hampered our qualitative evidence synthesis, while studies were defined as positive if the study results were statistically significant or clinically relevant. Clinical relevance was defined as an effect size of 0.5 or more. This implies that some studies, especially those with low statistical power, might have been incorrectly classified as not positive.

Generalizability to daily clinical practice

In this review, an attempt was made to assess the generalizability of the included studies to daily clinical practice. Poor generalizability to patients seen in daily practice is one of the limitations particularly associated with RCTs (88–90). Previous studies showed that patients with comorbid disorders are often excluded from trials (19,89). We have indications that the aggressive patient commonly seen in daily clinical practice was excluded from the evaluated trials because of the recruitment procedures depending on voluntary participation, the strict inclusion and exclusion criteria, and the sometimes inadequate resource population.

Recommendations for further research

As only weak evidence of efficacy was found, further research in this field is required. For future research, consensus on the use of aggression measurement scales should be reached, which might facilitate the conduct of meta-analytic pooling. The assessment of changes in aggressive behavior should be done with observer-rated scales. We suggest using both an incident-based scale, like the OAS (62) or SOAS (65) and a scale measuring behavioral and psychopathologic changes, like the SDAS (66).

Furthermore, the results of future trials should be more generalizable to daily clinical practice. More generalizable results can be achieved by conducting pragmatic trials (19,90). Pharmacoepidemiologic research might be another option to obtain evidence generalizable to daily clinical practice (88).

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Chapter 2.3

Trials assessing pharmacotherapeutical management of aggression in psychiatric patients: comparability with daily clinical practice of psychiatric longstay wards

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Abstract

Objective In a previous review of Randomised Controlled Trials (RCTs) on the pharmacotherapeutical management of aggression, it was shown that there is only weak evidence of effectiveness. In the present study we aim to determine comparability of patients included in these RCTs and patients of psychiatric long-stay wards.

Methods Exclusion criteria that were used in at least 20% of the RCTs were applied to a sample of aggressive inpatients from clinical practice, in order to find what proportion of these patients would be eligible to participate in the reviewed, high quality RCTs.

Results Only 30% of aggressive psychiatric patients as seen in clinical practice would be eligible to participate in a typical randomized controlled trial based on the most frequently applied exclusion criteria.

Conclusion The low comparability of patients included in RCTs with those seen in clinical practice may decrease the generalizability of the findings form RCTs to clinical practice.

Introduction

Aggression is an important issue in mental health departments, as it negatively influences the well being of both patients and staff workers and results in high costs (4,21). Pharmacotherapy is one of the tools used to prevent or reduce aggressive behaviour and incidents. Our group has shown that only weak empirical evidence is available for the effectiveness of pharmacotherapeutical management of aggression (18). This systematic review was restricted to Randomised Controlled Trials (RCTs) as these are considered to be the gold standard to obtain the most valid evidence for the effect of interventions (38). However, one of the observations from the review was that characteristic aggressive patients seen in clinical practice may be different from those included in RCTs, because of recruitment procedures depending on voluntary participation, strict inclusion and exclusion criteria, and sometimes small populations. This selection process may hamper the comparability of RCT populations to daily clinical practice patients, as has been shown by others, especially in psychiatric populations. Zimmerman (44), for example, showed that only 14% of depressed patients seen in daily practice would qualify for trial participation when applying exclusion criteria that are commonly used in RCTs. Another recent study showed that in patients suffering from epilepsy, less than thirty percent would qualify to participate in a standard RCT (39).

In the present study we aim to determine the comparability of patients in RCTs investigating the maintenance pharmacotherapy for patients to whom aggression is an ongoing problem, with patients of psychiatric longstay wards.

Methods

RCTs

In a previously published paper, we reviewed the literature for RCTs assessing the pharmacotherapeutical maintenance therapy of aggression (18). In brief, these trials were retrieved by searching Pubmed, EMBASE, Psyclit and Cochrane up to March 2004, using MESH-terms covering both "aggression" (including aggression-related symptoms like violence) and pharmacotherapy (including the different psychotropic drug classes). These RCTs (1-3, 5-13, 15-17,19,20,23-30, 32-37, 40-43) studied the pharmacological management of aggression in adult (18-65 year) psychiatric patients in general psychiatric settings. This means that RCTs applying to specialized psychiatric settings—like child psychiatry, mental retardation, and organic brain diseases—or to nonpsychiatric settings—like prisons—were not included in this review. From this review, only those RCTs of sufficient methodological quality, which was defined as a Jadad-score (22) of three or more, were selected for the present study.

The selected 31 RCTs (1-3, 5-8, 10-13, 17, 19, 20, 23-25, 27-30, 32-37, 40-43) with sufficient quality were reviewed for applied exclusion criteria.

The population sampled from clinical practice consisted of all patients of three long stay wards of Altrecht Mental Health Care Institute who engaged in aggressive behaviour during admission. The three participating wards were units for forensic psychiatry, a centre for intellectually disabled adolescents and adults with severe disruptive behaviour, and a ward for juveniles with externalizing behaviour disorders. Aggressive behaviour at these wards was continuously monitored and recorded by the staff using the Staff Observation Aggression Scale-Revised (SOAS-R) (31). Patients eligible for our study populations had all had been admitted for at least two weeks during the period September 2004 until December 2005**.** Patients with one or more aggressive incidents during the study period, as recorded with the SOAS-R, were selected.

For consenting patients, physical examination, medical history and laboratory values were determined during the first week of admission. These data as well as demographic information were extracted from the hospital records.

The study protocol was approved by the Institutional Review Board of the hospital.

Data analysis

All selected RCTs were reviewed and all exclusion criteria that were used in at least six (20%) of the 31 RCTs were selected. Subsequently, these criteria were applied to the sample of aggressive inpatients from clinical practice, in order to calculate what proportion of these patients would be eligible to participate in the reviewed, high quality RCTs. Lastly, characteristics of eligible patients were compared with characteristics of ineligible patients.

As the patients from clinical practice were all inpatients, a subanalysis, with the use of only the exclusion criteria used in at least 20% of the RCTs conducted in inpatient settings, was performed.

Results

RCTs

The RCTs were conducted in the following patient groups: schizophrenic patients (N=12 [39% of the RCTs]) and patients with cluster B personality disorder (N=12 [39% of the RCTs]), patients suffering from PTSD (N= 3 [10% of the RCTs]), depressive disorder (N=2 [7% of the RCTs]), ADHD (N=1 [3% of the RCTs]) and autistic disorder (N=1 [3% of the RCTs]).
The exclusion criteria extracted from the RCTs are presented in Table 1.

Table 1 Exclusion criteria used in the RCTs

Exclusion criteria	Percentage of all trials in which the criterion was used	Percentage of trials, conducted in inpatient setting, in which the criterion was used
Substance abuse (alcohol or drugs)	54.8	44.4
Abnormal routine laboratory values	51.6	66.7
Clinically relevant systemic somatic disorder (heart, renal, hepatic, neurological, asthma and COPD)	51.6	61.1
Pregnancy	38.7	33.3
Use of other psychotropics than the study drug	35.5	16.7
Lactating	32.2	27.8
Suicidal ideation	19.3	0.0
Without contraception	16.1	11.1
Unstable medical disorder	16.1	16.7
Organic brain disorder	9.7	38.9
Psychotherapy	9.7	0.0
Depot neurolepticum	9.7	16.7
Women	6.4	0.0
Men	3.2	0.0
History of psychiatric hospitalization	3.2	0.0
IQ < 75	3.2	5.6
Drug induced psychosis	3.2	5.6
Selfmutilation	3.2	0.0

A number of exclusion criteria, including "relevant somatic disorder", "physical disorder", "unstable medical disease" and "abnormal routine lab", were generally not well-defined. The authors of studies in which these exclusion criteria were not well-defined, were contacted by email for further specification of these criteria. Response rate was low (3 out of 15 = 20%). On basis of the responses and the other reviewed RCTs in which somatic illnesses or deviant laboratory values as exclusion criteria were defined more precisely, we decided to further specify the criteria as follows:

"relevant somatic disorder", "physical disorder" and "unstable medical disease" included neurological diseases, COPD and asthma, cardiovascular disease, liver disease and renal failure, whereas "abnormal routine lab" comprised deviant laboratory tests findings, including liver function, kidney function, thyroid function and haemogramme.

The exclusion criterion "the use of psychotropics other than the study medication" was used in 58% of the trials with borderline patients, but in none of the trials conducted in a study population consisting of schizophrenic patients.

Table 2 Clinical study sample

Characteristic	Patients with aggressive incident(s) (n=106)	
Age (mean, SD)	27.3	(10.4)
Aggressive incidents per month (mean, SD)	1.9	(4.2)
	N	**(%)**
Male sex	76	(71.7)
Diagnosis (DSM IV)		
Axis I		
Psychotic disorder	49	(46.2)
Mood disorder	11	(10.4)
Anxiety	6	(8.8)
Alcohol dependence/abuse	9	(8.5)
Drug dependence/abuse	27	(25.5)
Pervasive disorder	10	(9.4)
ADHD & disruptive behaviour	24	(22.6)
Other	11	(10.4)
Axis II		
Personality disorder	14	(13.2)
Mental retardation	40	(37.7)
Regular medication use		
Antidepressants	18	(17.0)
Antipsychotics	54	(50.9)
Benzodiazepines	33	(31.1)
Moodstabilizer	11	(10.4)
Somatic medication	33	(31.1)

Clinical practice sample

The clinical practice sample consisted of 106 aggressive patients. Patients' characteristics are displayed in Table 2. Exclusion criteria were applied in descending order of appearance in the trials. Current drugs and/or alcohol abuse was observed in 29% of the patients. Fourteen patients (13%) had a relevant somatic disorder. Furthermore, three patients (3%) refused to undergo a physical examination, which would be reason for exclusion in an RCT. Abnormal routine lab was observed in 13% of the patients, whereas 5% of the patients refused to give a blood sample. No patients were pregnant or lactating. Finally, in several studies patients were excluded if other psychotropics were used concomitantly with the study drug. We assumed that patients from our study sample using two or more psychotropics would not likely be switched to only one study-drug.

Therefore, from our study sample patients using more than one psychotropic, i.e. almost one third (34%), were considered ineligible for a trial.

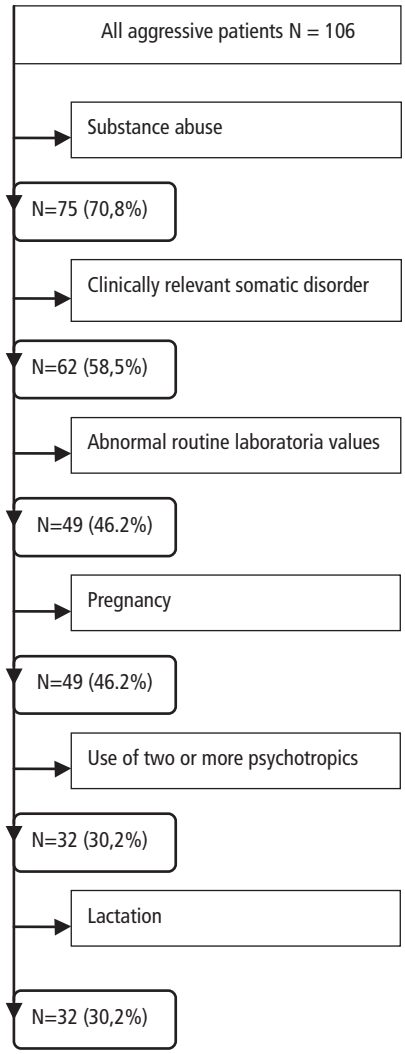

Figure 1 Sequential application of exclusion criteria to the whole group of patients.

With the application of these criteria on the study population, only 30% of the patients would be eligible for trial participation (Figure 1). As use of other psychotropics was not a frequently used exclusion criterion in the RCTs conducted in patients with schizophrenia, we also calculated the percentage of eligible schizophrenic patients, without application of this criterion, which resulted in a percentage of 43% of patients that would be eligible.

Lastly, in the subanalysis in which only exclusion criteria of the RCTs conducted in inpatients setting were applied to the clinical practice sample, 46% of patients appeared to be eligible.

Table 3 Comparison of eligible and ineligible patients

Characteristic	Eligible patients		Ineligible patients		p value
	N	(%)	N	(%)	
Age (mean, SD)	23.5	9.9	28.9	10.3	0.003
Aggressive incidents per 100 days (median)	4.2		2.5		0.19
Severely aggressive	28	(87.5)	55	(74.3)	0.13
Male sex	20	(62.5)	56	(75.7)	0.17
Diagnosis (DSM IV)					
Axis I					
Psychotic disorder	11	(34.4)	38	(51.4)	0.11
Mood disorder	4	(12.5)	7	(9.5)	0.64
Pervasive disorder	6	(18.8)	4	(5.4)	0.06
ADHD & disruptive behaviour	11	(34.4)	13	(17.6)	0.06
Axis II					
Personality disorder	2	(6.2)	17	(23)	0.04
Mental retardation	10	(31.2)	30	(40.5)	0.37

Eligible versus ineligible patients

The eligible patients were compared with the ineligible patients, results of this comparison are shown in Table 3.

Eligible patients were significantly younger and were less frequently diagnosed with a personality disorder. Concerning the frequency and severity of aggression, no differences were observed between eligible and ineligible patients.

Discussion

The current results suggest that, based upon the most frequently applied exclusion criteria, only 30% of aggressive psychiatric patients as seen in clinical practice would be eligible to participate in a typical randomized controlled trial investigating the pharmacological maintenance treatment of aggression. This finding is in line with the proportions reported in two previous studies, in which 14% and 30% of patients from clinical practice were found to be eligible for trial participation in a clinical practice population treated for depression and epilepsy, respectively (44,39).

These findings warrant the conclusion that the evidence for the pharmacological management of aggression not only appears to be weak (18), but that, additionally, the patients in trials are different from the patient of clinical practice, or at least different from typical psychiatric long-stay inpatients. Subsequently this raises the question if the trial outcomes are generalisable to clinical practice. It is quite well imaginable that they are not. For example, it is likely that more somatic comorbidity influences the generalizability of trials, e.g. due to the use of co-medi-

cation. Furthermore, comparison of the group of the eligible with the non-eligible patients shows that the eligible patients differ from the non-eligible patients, at least for diagnosis and age.

In addition to the exclusion criteria applied, other characteristics of the evaluated RCTs are likely to decrease the comparability of trials to clinical practice. Firstly, previous research suggests that aggressive patients are less likely to give informed consent (14). This might lead to an underrepresentation of severely aggressive patients. Furthermore, the setting of many RCTs (~40% in outpatient departments) and the recruitment methods (e.g. advertisement) might also have contributed to an underrepresentation of severely aggressive patients in the RCTs. It is well imaginable that the aetiology of aggression of severely aggressive patients differs from the aetiology in mildly aggressive patients, thereby requiring different pharmacotherapeutical strategies.

In conclusion, it is likely that the low comparability of the patients in RCTs with the patients from practice affects the generalizability of the efficacy of trial medication and observed side effects. However, with the available data we were not able to investigate this. To investigate this, other research, such as conducted by Wisniewski et al. (45), is needed. In that study the researchers showed that depressive patients who would be ineligible for a phase III trial with antidepressants, experienced more severe side effects and had lower remission and response rates compared to the eligible patients.

From a clinical point of view we therefore conclude that it might be understandable that with only weak evidence for efficacy, psychotropics are used (off-label) in an attempt to manage such a difficult behaviour as aggression. However, to our point of view, prescribers should be well aware of the limited available evidence with a probable low generalizability to clinical practice, and certainly stop the medication if no effect is observed.

This study has some limitations. The criterion "multiple psychotropic use" was observed in the trials conducted in populations consisting of patients with cluster B personality disorder, but not in the trials conducted in populations consisting of schizophrenic patients. The percentage of patients that could be included in a study would increase to 46% if multiple psychotropic use would be allowed. This suggests that an analysis, stratified for diagnosis would be more appropriate. However, the number of included trials was not enough to conduct such an analysis.

Furthermore, because the methodology of the trials was not always clearly described, we may have interpreted the criteria concerning somatic disorders and abnormal routine laboratory values not strictly enough or too strictly when cut-off points were not mentioned in the RCTs. Future studies possibly could give more insight, with the current regulations binding researchers to publish their study protocols in an internet database.

Conclusion

With an eligibility percentage of 30-46%, we conclude that the patient comparability of trials, investigating the pharmacological management of aggression, to clinical practice is low. Furthermore, other RCT characteristics suggest that patients displaying severe aggression are not eligible in RCTs. The low comparability may decrease the generalizability of RCT findings to clinical practice.

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3

Treatment in practice

Chapter 3.1

The correspondence between the Staff Observation Aggression Scale-Revised and two other indicators for aggressive incidents

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Abstract

Objective Previous research has shown good psychometric properties of the Staff Observation Aggression Scale-Revised (SOAS-R). However, it has never been investigated what proportion of aggressive incidents occurring in facilities is documented with the SOAS-R. Furthermore, if incidents are underreported, the consequences for the categorization of clients into aggressive and non-aggressive subgroups based on the SOAS-R are unknown.

Methods In four inpatient psychiatric facilities for adults with mild intellectual disabilities, aggressive incidents were documented with the SOAS-R and two other indicators of aggressive incidents: the daily staff reports on clients' behavior and reports on of the use of restraints.

Results Less than half of the incidents documented with the staff and restraint reports were also documented with the SOAS-R. On the other way around, however, it was also found that a substantial proportion of incidents reported on SOAS-R forms were not documented in the daily staff reports, which points to a more general problem of underreporting aggressive behavior. Apart from that, categorization of clients into an aggressive and a non-aggressive subgroup with SOAS-R data collected during one month or longer corresponded largely with the categorization based on both other indicators.

Conclusion This study showed that underreporting of aggressive incidents is likely to occur with the SOAS-R, making the instrument less suitable to assess absolute aggression incidence in facilities. Still, the SOAS-R seems a good instrument to categorize clients into aggressive and non-aggressive subgroups. Ways to improve the compliance of the ward team to document all aggressive incidents are addressed in the Discussion section of this article.

Introduction

The staff observation Aggression Scale-Revised (SOAS-R) (1, 2) has been developed to assess inpatient aggression. The SOAS-R is an incident-based scale, and it is supposed to be completed every time a staff member witnesses aggressive behavior by a client. In a broad variety of psychiatric facilities, the SOAS-R has been used to study incidence, causes, and determinants of inpatient aggression (see, for a review, (3)). Besides, the SOAS-R has been used to categorize clients into aggressive and non-aggressive subgroups (4). A recent review about the psychometric properties of the SOAS-R suggested fair to good interrater reliability and validity for SOAS-R assessments (3). For example, two raters judging the same incident come to comparable severity ratings (5, 6) and significant correlations are observed with other methods for assessing aggressive behavior (6, 7). When using the SOAS-R, the underlying assumption is that all aggressive incidents occurring in inpatient facilities are documented with it. If documentation is incomplete, this may have implications for the reliability and validity of the categorization of clients into aggressive subgroups based on the SOAS-R. In the fore-mentioned review of SOAS-R studies, it was concluded that "there have not been any studies conducted on this potential reliability problem (3). Furthermore, it was assumed by the authors that especially milder forms of aggressive behavior may run a risk of being underreported.

In this study, we examined the correspondence between the SOAS-R and two other indicators of inpatient aggression, namely, the daily staff reports on clients' behavior and the documentation of the use of restraints, in four treatment facilities for adults with mild intellectual disability (ID) and severe behavioral and/or psychiatric problems. The research questions were the following: (a) Are all incidents documented by both other means also reported with the SOAS-R, and if not, are some types of incidents, that is, mild or severe, selectively missed by the SOAS-R? (b) Is the categorization of clients into aggressive and non-aggressive subgroups based on SOAS-R data comparable with categorization based on both other indicators?

Methods

Setting

This study was conducted in four inpatient treatment facilities, together including 138 beds, for adults with mild ID and severe behavioral and/ or psychiatric problems. Data of 76 clients, 25 women and 51 men with an average age of 25.8 years (SD = 7.6 years), were included in this study.

Assessments

The SOAS-R

In the SOAS-R, aggressive behavior is defined as "any verbal, non-verbal, or physical behavior that was threatening (to self, others or property), and/or physical behavior that actually did harm (to self, others, or property)" (8). The SOAS-R is composed of five columns: (a) antecedents provoking the incident (provocation), (b) aggressive means used by the client, (c) target of aggression, (d) consequence(s) for victim(s), and (e) measures taken to stop the incident. Every time a staff member witnessed aggressive behavior displayed by a client in one of the four facilities under study, an SOAS-R form was supposed to be completed.

Autoaggressive incidents were excluded, that is, incidents in which the "patient self" was the target of the aggressive incident. The other incidents reported with the SOAS-R were categorized as being either "mild" or "severe." Incidents were categorized as mild if the targets were nothing/ nobody or objects or if the aggressive means used exclusively consisted of verbal aggression. Incidents were categorized as severe if targets were persons, and the means used during the incident concerned some form of physical aggression. The SOAS-R was implemented for a 6-month trial. In this study, SOAS-R data of the last 3 months of the trial (Months 4–6) were used.

Alternative indicators of inpatient aggression

Restraint forms

According to the Dutch law, the use of involuntarily administrated restrictive measures has to be recorded by the doctor in charge on a restraint form. Restrictive measures include mechanical restraints, involuntarily medications, and seclusion. Restraint forms of each facility over a period of 3 months were requested, that is, Months 4 to 6 of the SOAS-R trial. This yielded a total number of 96 restraint forms. Two raters, a research assistant and a clinical psychologist, independently judged whether the restraint was applied to stop an—outwardly directed—aggressive incident. For one form (1%), no agreement was reached; it stated that "X got frantic and started slamming with doors." Both raters judged differently whether this concerned an aggressive incident or not. This form was excluded from analyses. The description of the behavior of clients that leads to the use of restrictive measures on the forms was judged not to be detailed enough to be able to make distinctions between mild and severe incidents.

Daily staff report

The daily staff report is a short report about the behavior of each client during each shift, which is written by a (psychiatric) nurse to facilitate transference of information between shifts. Of a random selection of 64 clients, the daily reports during the fourth month of the SOAS-R trial were evaluated independently by two raters, that

is, a research assistant and a psychiatrist. Daily reports were screened for aggressive incidents, as defined in the SOAS-R. These aggressive incidents were categorized as mild or severe using the same criteria as for the incidents reported with the SOAS-R. Disagreements, less than 5% of all incidents, concerning the interpretation of the daily reports between raters were discussed and resolved.

Procedure

Before the implementation of the SOAS-R registration in each facility, the SOAS-R was introduced to staff members on all participating wards. The importance of complete documentation of all aggressive incidents was explained, and instructions on how to use the SOAS-R forms were provided. The definition of aggressive behavior as printed on the SOAS-R forms was also discussed and explained to the ward staff. Writing daily reports and completing restraint forms were both part of general procedures in the facilities. No additional instructions were given. Staff members responsible for the daily reports and restraint forms did not know that these reports would be used to examine the reliability of the SOAS-R. The raters, who assessed the daily reports and restraint forms, were unaware of the SOAS-R results.

Analyses

Correspondence on incident level

To study correspondence on the incident level, we examined how many of the incidents reported in the daily reports and on restraint forms were also documented with the SOAS-R; this was expressed as a percentage of all incidents reported in the daily reports and on the restraint forms. To investigate if SOAS-R reporting was dependent on participating facilities, we compared facilities with regard to these percentages using the χ^2test. Besides, we examined whether the type of incident reported in the daily reports, that is, severe or mild, was related to whether or not an SOAS-R form was completed, again using a χ^2 test. Vice versa, we examined whether the type of incident reported with the SOAS-R, that is, severe or mild, was related to whether or not this incident was reported in the daily report. We could not perform the above-mentioned analyses with the restraint form data as we did with the daily report data. Main reasons for this are that the restraint form incidents could no be categorized into mild and severe and not all aggressive incidents occurring in the facilities are expected to be documented with restraints forms, that is, only incidents that led to involuntarily restraints are recorded with it.

Correspondence on client level

To examine correspondence on the client level, we assessed the number of clients with at least one restraint form and at least one SOAS-R report during the assessment period of 3 months; this was expressed as a percentage of all clients with at

least one restraint form. On the basis of the daily reports data, clients were assigned either to a non-aggressive group, that is, clients caused no aggressive incident, or to an aggressive group, that is, clients caused at least one incident during the month the daily reports were evaluated. We determined correspondence between this categorization and the equivalent categorization based on the collected SOAS-R data during the same month and during 3 months. Kappa value was calculated as a measure of agreement and evaluated according to the criteria of Landis and Koch (9).

Results

The evaluation of the daily reports of 1 month, the fourth month of the SOAS-R trial, of 64 clients resulted in 109 aggressive incidents. In the corresponding month, for these 64 clients, 56 incidents were documented with the SOAS-R. In the 3 months the restraint forms were evaluated, Months 4–6 of the SOAS-R trial, 54 restraint forms were related to aggressive incidents, in which 20 clients were involved.

Correspondence on incident level

For 32 (29.4%) of the 109 incidents documented in the daily reports, an incident documented with the SOAS-R on the same day on the same client was available. The four facilities did not differ with regard to this percentage, χ^2 (3) = 5.44, P = .14. Of the 77 aggressive incidents that had been documented exclusively in the daily reports but not with the SOAS-R, 51 (66%) incidents were categorized as being mild and 26 (34%) as being severe; of the 32 incidents documented with both the daily reports and the SOAS-R, categorization of incidents based on the daily reports resulted in 19 (59%) of the incidents categorized as mild and 13 (41%) as severe. Differences in these percentages did not reach statistical significance, χ^2 (1) = .46, P = .49. On the other way around, it was found that not all incidents documented with the SOAS-R, that is, 24 (43%) of the 56, were documented in daily reports. Of the 32 incidents documented with both methods, according to the categorization of incidents based on the SOAS-R, 22 (69%) of the incidents could be considered as being severe and 10 (31%) as being mild. Of the 24 incidents only documented with the SOAS-R, 15 (63%) were categorized as severe and 9 (37%) as mild. The difference in these percentages was not statistically significant, χ^2 (1) = .24, P = .63. For 22 (40.7%) of the 54 aggressive incidents documented with the restraint forms, an SOAS-R form was available. In one unit, no restraint forms related to aggressive behavior by clients. Between the other three facilities, no significant difference in the percentage of restraint forms for which an SOAS-R form was available was observed, χ^2 (2) = 2.75, P = .25.

Correspondence on client level

Thirty (46.9%) of the 64 clients of whom the daily reports were evaluated could be considered aggressive, that is, at least one aggressive incident was documented in the daily report. According to the SOAS-R data collected during the same month, 19 (63.3%) out of these 30 clients could be considered aggressive, that is, at least one aggressive incident was documented with the SOAS-R. In Table 1, the correspondence between the categorization of clients into an aggressive versus a non-aggressive group based on the daily reports and SOAS-R data documented during the same month is presented. With the daily reports categorization as reference, 11 clients were incorrectly categorized as non-aggressive with the SOAS-R data (Table 1). Overall, the SOAS-R classification corresponded with the daily reports data classification for 52 (81%) of the 64 clients. The kappa value for this agreement was .62, indicating good agreement. However, it should be noted that the observations of the aggressive behavior could have taken place at different moments in time. Categorization improved when 3 months, instead of 1 month, of SOAS-R documentation was used to categorize clients, that is, this resulted in 4 clients, in contrast to 11, being incorrectly categorized as non-aggressive (Table 1). In other words, 26 (86.7%) of the 30 clients who had been aggressive according to the daily staff reports had also been observed to behave aggressively by means of the SOAS-R.

The kappa value for the overall agreement was .75, indicating good agreement (56 [88%] of the 64 clients were correctly classified).

Of all 20 clients (100%) for whom one or more restraint forms were available, there was also one or more incidents documented with the SOAS-R during the corresponding 3-month period.

Table 1 number and percentage of clients categorized aggressive versus non-aggressive groups according to the daily reports data and soas-r data and soas-r categorization based on data collected during 1 and 3 months

	SOAS-R categorisation				
	1 month		3 months		
Daily Reports categorization	Non-aggressive*	Aggressive †	Non-aggressive*	Aggressive †	Total
Non-aggressive*, n (%)	33 (97.1)	1 (2.9)	30 (88.2)	4 (11.8)	34
Aggressive †, n (%)	11 (36.7)	19 (63.3)	4 (13.3)	26 (86.7)	30
Total	**44**	**20**	**34**	**30**	**64**

*** Clients without documented aggressive incidents.**
† Clients with one or more documented aggressive incidents.

Discussion

Results of this study indicate that when the SOAS-R is used to assess the incidence of aggressive incidents in inpatient facilities for individuals with mild ID, underreporting forms a threat to the reliability of the assessments. Less than half of the aggressive incidents documented by other means (i.e., daily reports and restraint forms) were also documented with the SOAS-R. However, also in the daily reports, not all incidents were reported; approximately 4 (i.e., 42.9%) out of 10 incidents that were documented with the SOAS-R were not reported in the daily reports about clients' behavior. These results suggest that underreporting of aggressive incidents poses a general problem. Clearly, the reliability of any aggression observation method relies on the preparedness of the ward staff to record every aggressive occurrence. However, we assume that the ward staff in this study in this respect did not differ from the ward staff in other studies. The ward staff in the current study seemed motivated to record aggressive behavior, and no significant differences between wards were discovered as far as their documentation "performances" with the SOAS-R were concerned. That is, no statistically significant differences in the percentages of daily report incidents and restraint form incidents, for which an SOAS-R incident on the same client on the same day was available, were found between the facilities. Besides, the derived annual number of 10.5 incidents per year per client found in this study (56 incidents documented with the SOAS-R in 1 month / 64 clients × 12) is comparable to the annual number of 9.3 incidents per client found on acute psychiatric wards reported by Nijman (3).

It has been suggested that especially mild incidents may run the risk of not being documented with the SOAS-R (3, 10); however, this appears not to be supported by the present findings. The proportion of severe and mild incidents was not different for the daily report incidents documented (59% mild) and daily reports not documented (66% mild) with the SOAS-R. Furthermore, almost 60% of the aggressive incidents that resulted in involuntarily restraints, and therefore may be considered relatively severe, were not documented with the SOAS-R.

An explanation for the underreporting might be that a staff member becomes reluctant to complete an SOAS-R form if a patient frequently shows the same pattern of aggressive behavior, especially when the staff member knows how to intervene and does not feel threatened anymore. Alternatively, reporting of aggressive incidents might wane as time progresses and no additional (standardized) efforts are made to keep the ward team aware of the necessity to document incidents. This may be particularly true for the SOAS-R reporting system in case it is not the regular way of reporting aggressive incidents. New or temporary staff members will not have been present at the instruction about the SOAS-R and thus might be less attentive on completing SOAS-R forms, whereas they generally will be used to,

and aware of, the necessity of writing daily reports and completing the mandatory restraint forms.

In contrast to the results on incident level, the SOAS-R results with regard to the categorization of clients into aggressive and non-aggressive groups were more promising. With the daily reports data as reference, 81% of the clients were correctly classified with the SOAS-R data registered during the same month. The kappa statistic suggested good agreement between both modes of categorization. The number of clients categorized incorrectly as non-aggressive was further reduced when using a longer period of SOAS-R data to categorize clients, as the results concerning the restraint forms and the categorization with the SOAS-R over a period of 3 months indicated.

Limitations

A limitation of this study is that the two indicators used to compare the SOAS-R data with do not reflect the true incidence of aggressive incidents in facilities. As mentioned previously, not all incidents documented with the SOAS-R were reported in the daily reports, and incidents documented with the restraint forms only concern those incidents that were followed by the use of involuntarily restraints. The results of this study only indicate that by using the SOAS-R, an underreporting of the true incidence of aggressive incidents can be expected. However, the same seems to be true for other ways of reporting aggressive incidents, such as daily staff reports. Because of this, the absolute amount of underreporting cannot be estimated from these results. As underreporting of aggressive incidents appears to be a general problem and no significant differences between the wards in documentation compliance were found, data obtained with the SOAS-R may still be valid for comparison purposes between wards and institutions with respect to their relative levels of aggressiveness.

Recommendations

The substantial underreporting of aggressive incidents with the SOAS-R, but also in the daily reports, observed in this study, stresses the importance of reminding staff repeatedly and structurally about the necessity to record all aggressive behavior. An effective way to prevent underreporting of aggression with the SOAS-R that is used in practice is to put aggression and its documentation as a fixed item on the agenda of the weekly or even the daily team meetings (i.e., the shift transference meetings). By spending a moment at the beginning of such meetings on whether aggressive incidents have occurred and, if so, whether they have been documented adequately, the focus on documenting aggression will be maintained.

For studying the effects of interventions, however, it seems advisable that the use of incident-based aggression observation tools is combined with a period-based aggression measurement scale, such as the Social Dysfunction and Aggression Scale

(11), which has to be completed at predetermined times. On the other hand, compared with period-based aggression scales, incident-based aggression assessments may have the advantage that they provide more opportunities to study the specific circumstances and temporal factors involved in triggering aggressive outbursts (12). Possibly, combining SOAS-R with weekly performed assessments such as the SDAS would be the most optimal way to assess inpatient aggression. To assess the absolute number of aggressive incidents in facilities, probably, researcher-based observations on the ward for a certain period could serve as a criterion. However, direct observation can be an intrusive technique and may also influence behavior on a ward.

Aggressive incidents in psychiatric patients with behavioural problems trigger reactive prescribing behaviour

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Chapter 3.2

Aggressive incidents in psychiatric patients with behavioural problems trigger reactive prescribing behaviour

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(submitted)

Abstract

Objective: To investigate the association between aggressive incidents in psychiatric patients and changes in prescribing of regular medication.

Methods: A 16-months prospective observational study was conducted in three psychiatric wards where all aggressive incidents were prospectively registered using the SOAS-R scale. Patients with and without aggressive incidents were compared with respect to the frequency (expressed as incidence density per personyear (ID)) of psychotropic and somatic medication changes (start, discontinuation, dosage-increase, dosage-decrease, switch to another drug within the same therapeutic drug class and formula change). Furthermore, in aggressive patients only, the frequencies of changes in psychotropic medication a) during a day before versus a day following episodes of aggression, b) during episodes of aggression versus remaining follow-up time, i.e. non-aggressive episodes, were compared.

Results: A total of 106 (61%) out of the 174 included patients exhibited 1107 aggressive incidents. For aggressive patients 653 psychotropic medication changes were observed versus 167 changes for non-aggressive patients (ID: 8.6 and 5.9 per personyear, respectively; ID Ratio (IDR): 1.5, 95%CI [1.3-1.8]). Overall, for aggressive patients, significantly higher IDs were observed for start of psychotropic medication and dosage-increases (IDR 1.8, 95%CI 1.2-2.6 and 2.1, 95%CI 1.4-3.1, respectively); IDs for other changes were non-significantly increased. ID of somatic medication changes for aggressive patients and non-aggressive patients did not differ significantly (IDR 1.2 95%CI 0.8-1.9). Within the group of aggressive patients, the number of changes on the day before and following aggressive episodes did not differ. However, in the period of one day before untill one day following aggressive episodes, an ID of 19.5 per personyear was observed, versus 7.8 during the remaining aggression-free follow-up time (IDR = 2.5; 95% CI 2.0-3.1).

Conclusion: Regular medication patterns of aggressive patients in general are frequently subject to change during their hospitalisation. Apparently, difficult patient behaviour, such as aggression, triggers reactive prescribing behaviour.

Introduction

Several pharmacoepidemiological studies have shown that medication changes - such as dosage changes, switching, starting, or stopping of medication- can be either the heralds of or the reaction to disease or treatment related trouble, such as the onset of a disease, treatment failure, worsening of disease, or the occurrence of side effects (1-3). Stuffken et al., for example, found an increased initiation of benzodiazepine prescriptions during the three months prior to admission in a general hospital. (1) They hypothesized that the increased prescriptions were a reaction to mental manifestations linked to an underlying physical disease, which may occur before hospitalization. Examples of an increased frequency of medication changes associated with disease or treatment related trouble, in mental health care include antipsychotic polypharmacy for schizophrenic patients with a high relapse rate or comorbidity (3) and frequent switching of antidepressants for patients poorly responding to therapy (2).

In one of our previous studies, we found that aggressive behaviour of long-stay psychiatric patients - a particularly difficult to manage troublesome behaviour with large impact on health care workers and patients- is associated with a significant increase in the use of as-needed medication, not only psychotropics but also medications for somatic disorders such as analgesics (5). The prescribing and administration of psychotropic as-needed medication as a reaction to aggressive incidents is not surprising; it will often be administered to sedate the patient as a response to aggressive behaviour. One might hypothesize that signs of imminent aggression or aggressive incidents, given their impact on patients and their environment, trigger changes not only in as needed medication, but also in regular medication, either as a rational effort to treat aggression or possibly as a behavioural reaction of the physician 'to do something'. In that case, more changes are likely to occur following aggressive incidents. Therefore, in this study we aim to quantify and specify the type of the changes in the prescribing of regular psychotropic and somatic medication use of aggressive psychiatric long-stay patients, compared to non-aggressive psychiatric long-stay patients. Furthermore, the temporal relationship between the occurrence of aggression and changes in prescriptions of medication is investigated.

Methods

Setting, design and subjects

This observational study was conducted on three wards of the Altrecht centre for mental healthcare. These three wards have a total capacity of 90 beds with a mixed patient population (i.e., forensic psychiatric patients, patients with severe psychiatric disorders combined with mild learning disabilities, and juveniles with severe behav-

ioural problems) and were selected for the current study because of the anticipated high prevalence of aggressive behaviour.

All patients admitted to these wards, with at least one week of their admission during the studyperiod, were included in the study. Start of follow-up was defined as either the start of the studyperiod (September 2004), or the day of admission, whichever came first. Follow-up ended either on the day of discharge from the participating wards or the end of the study period (December 2005).

Patients were informed about the study and included if they did not object to participation. The Institutional Review Board of the mental health care centre approved the study protocol.

Data collection

Aggressive incidents were prospectively documented using the Staff Observation Aggression Scale Revised (SOAS-R), a widely used instrument to measure the frequency, severity and nature of aggression (6). Aggressive incidents were clustered into one episode of aggressive incidents if the time-period between incidents was shorter than three days. Patients who had been outwardly aggressive at least once during the study period, as recorded with the SOAS-R were categorized as aggressive, patients without aggressive incidents during the study period as non-aggressive control patients. Medication prescriptions of the participating patients were extracted from the pharmacy database of the hospital. In this database, information on drug prescribing is registered on an individual patient level, including the name of the drug, start and stop dates of the administration, dosages, and the name of the prescriber. Additional background data concerning the patients included in the study were collected from the hospital administration database. Data were directly anonymized by one of the researchers (LG), who also works as a medical doctor in the hospital.

Outcome

The outcome of interest was a change in regular medication (psychotropic as well as somatic). Regular medication, in contrast to as needed medications, was defined as medication administered regularly according to a dosing-scheme. A medication change was defined as either a start of a new medication, a discontinuation, a dosage increase or decrease, and a switch from one drug to another of the same pharmacotherapeutical drug class, and a change in formulation (see Table 1). Drugs were classified into psychotropic and somatic drugs. The psychotropic drugs were subclassified into the following four groups: antidepressants, antipsychotics, benzodiazepines, and moodstabilizers (valproate, lithium and carbamazepine).

Table 1 Definitions of changes investigated

Start	Start of drug administration. An administration-free period of at least seven days between a possible previous administration-period of the same drug was required.
Discontinuation	Discontinuation of drug administration. An administration-free period of at least seven days between a possible next administration-period of the same drug was required.
Dosage increase	Increase of the Prescribed Daily Dosage
Dosage decrease	Decrease of the Prescribed Daily Dosage
Switch	Change to another drug within the same pharmacotherapeutical drug class. The maximal period between the discontinuation of the first drug and the start of the other drug was 7 days
Formulation change	Change to another formulation. Formulations comprise: parenteral, oral tablet/ capsule, oral solution and orodispersable tablets

Data analyses

Incidence densities (IDs) of medication changes, i.e. the total number of medication changes divided by the total follow-up time, for the group of aggressive and non-aggressive patients were calculated. The IDs for the two groups were compared to each other and expressed as Incidence Density Ratios (IDRs) with corresponding 95% Confidence Intervals (95%CI). IDRs for psychotropic and somatic medication were calculated separately. Furthermore, for psychotropic medication subanalyses were performed for the different types of medication changes, and for the different therapeutical drug classes.

Change in total number of psychotropics, from start of the study to end of the study was calculated. Changes from start to end of the study for aggressive patients were compared with non-aggressive patients.

In order to investigate the time-relationship between aggressive incidents and medication changes, the number of medication changes one day before an aggressive incident or episode of aggressive incidents were compared with the number of medication changes during one day following this aggressive incident or episode, using the Wilcoxon signed rank test.

Results

Patients

In the study period, 176 patients were hospitalized for more than one week and therefore could be included in the study sample. Two of them objected to participation and were excluded from the study. At the end of the 15-month observation period, 106 of the 174 included patients (61%) turned out to have displayed aggressive behaviour and were responsible for a total of 1,107 outwardly directed aggressive

Table 2 Characteristics of the study population

Characteristic	Patients with aggressive incident(s) (n=106)		Patients without aggressive incident(s) (n=68)		p value
	Mean	(SD)	Mean	(SD)	
Age (mean, SD)	27.3	(10.4)	29.5	(8.7)	.04
Median duration of follow-up (days)	260	(154.2)	151.1	(142.8)	.00
	N	(%)	N	(%)	
Male sex	76	(71.7)	54	(79.4)	.25
Diagnosis (DSM IV)					
Axis I					
Psychotic disorder	49	(46.2)	41	(60.3)	.07
Mood disorder	11	(10.4)	7	(10.3)	.53
Anxiety	6	(8.8)	6	(5.7)	.42
Alcohol dependence/abuse	9	(8.5)	8	(11.8)	.48
Drug dependence/abuse	27	(25.5)	19	(27.9)	.72
Pervasive disorder	10	(9.4)	8	(11.8)	.62
ADHD & disruptive behaviour	24	(22.6)	5	(7.4)	.01
Other	11	(10.4)	3	(4.4)	.16
Axis II					
Personality disorder	14	(13.2)	10	(14.7)	.78
Mental retardation	40	(37.7)	23	(33.8)	.60
Regular medication users at inclusion					
Antidepressants	18	(17.0)	11	(16.2)	.90
Antipsychotics	54	(50.9)	41	(60.3)	.23
Benzodiazepines	33	(31.1)	21	(30.9)	.97
Moodstabilizer	11	(10.4)	4	(5.9)	.30
Somatic medication	33	(31.1)	22	(32.4)	.87

incidents during the study period. These aggressive incidents were clustered into 624 episodes of aggression.

Aggressive patients were significantly younger and had a longer follow-up period compared to non-aggressive patients (Table 2). Concerning the diagnostic distributions of both groups, significant differences in the frequency of drug abuse and ADHD or disruptive behaviour disorder were observed. At baseline, however, there were no differences in use of psychotropics between both groups (see Table 2).

Medication changes

During the study period, 820 changes in regular psychotropic medication were observed in 143 patients; 653 took place in 94 aggressive patients, and 167 in 49 non-aggressive patients (ID: 8.6 and 5.9, respectively; IDR: 1.5, 95% CI 1.3-1.8; see table 3). A subanalysis for the different changes in psychotropic medication revealed that in the group of aggressive patients, more frequently new drugs were started and more frequently drug dosages were increased.

Table 3 Medication changes per drug class

	Incidence density per personyear			
	Aggressive patients	Non-aggressive patients	IDR	95% Confidence interval
Any psychotropic	**8.6**	**5.9**	**1.5**	**(1.3 - 1.8)**
Antidepressants	0.8	0.6	1.3	(0.8 - 2.2)
Antipsychotics	3.8	2.6	1.5	(1.1 - 1.9)
Benzodiazepines	2.8	1.9	1.5	(1.1 - 2.0)
Moodstabilizers	0.6	0.5	1.3	(0.7 - 2.3)
Start	2.0	1.2	1.8	(1.2 - 2.6)
Discontinuation	1.8	1.4	1.3	(0.9 - 1.9)
Dosage increase	2.3	1.1	2.1	(1.4 - 3.1)
Dosage decrease	1.9	1.8	1.1	(0.8 - 1.5)
Switch	0.3	0.2	1.4	(0.5 - 3.7)
Formulation change	0.3	0.2	1.6	(0.7 - 3.9)
Somatic medication	**1.3**	**1.04**	**1.2**	**(0.8 – 1.9)**

No significant differences for the other types of medication changes were observed (see Table 3). Most changes occurred within the pharmacotherapeutical drug classes of antipsychotics and sedatives; these were also the most frequently prescribed types of drugs (see Table 2).

Additionally, per patient, the change from baseline to the end of the study for the used number of psychotropics were calculated. These changes for aggressive patients were compared with non-aggressive patients. The change in number of used psychotropics ranged from -4 to 3 (mean -0.09, median 0.00) and from -3.00 to 1.00 (mean -0.20, median 0.00) for aggressive and non-aggressive patients, respectively (not statistically significant difference: $Z = -0.89$, $p = 0.40$). For somatic medication a total of 118 changes were observed resulting in an ID for aggressive and non-aggressive patients of 1.3 and 1.0, respectively (IDR 1.2, 95% CI 0.8-1.9) (see Table 3).

Temporal association between aggressive incidents and medication changes

In the time period of one day before and following aggressive episodes along with the time period of the aggressive episodes, an ID of 19.5 per personyear was observed, versus 7.8 during the remaining aggression-free follow-up time (IDR = 2.5; 95% CI 2.0-3.1).

Also during the aggression-free follow-up time of aggressive patients more changes took place than during the follow-up time of non-aggressive patients (ID = 7.8 and 5.9 respectively, IDR = 1.3; 95% CI 1.1-1.6).

Discussion

The present results indicate that for patients displaying aggressive behaviour, regular psychotropic medication is frequently subject to change, especially in the time window of 24 hours around aggressive episodes. Starting new psychotropic medication and dosage-increases in particular occur more frequently in regular medication regimens of aggressive patients. Other changes, like discontinuation of regularly prescribed medication, medication switches, and formulation changes do not appear to occur more frequently in aggressive patients. This shows that aggressive patients in general receive an increasing number of medications during their admission. Apparently, difficult behaviour, like aggression, triggers reactive prescribing behaviour, leading to increased use of medication.

The question is why medication changes occur more frequently for aggressive patients. As relatively more changes took place during or directly around aggression episodes -compared to the remaining follow-up time- changes in medication might be an attempt to prevent or stop aggressive incidents. In contrast to our previous study, in which aggression was found to be associated with more administrations of as-needed medication in the three hours following aggressive incidents (4), the increase in changes shortly following aggressive episodes was not significant. This could well be explained by the presumption that if regular medication is changed in a reaction on aggression or imminent aggression, this is most likely to occur when the treating physician is on duty, whereas aggression can occur any time; by day and night, week and weekend. Furthermore, changes in regular medication are to be discussed with the patient beforehand, which generally may be difficult directly after an aggressive incident.

However, medication changes as a (direct) reaction on the occurrence of aggression is an inconclusive explanation, as during the aggression-free follow-up of aggressive patients, also an increased number of changes was observed, compared to the follow-up time of non-aggressive patients. Possibly, the regularly prescribed medication is increased by the physician with the aim of reducing more general patterns of agitated and disruptive behaviour that may be more prevalent in the aggressive patient group in between aggressive incidents.

Alternatively, an explanation might be that the increased number of changes observed in the group of aggressive patients reflects the treatment of severe or worsening psychopathology -which has been shown to be associated with aggression in some studies (6)- instead of the (direct) pharmacological management of aggression.

Despite the high number of pharmacological interventions in aggressive patients, the present study, as well as earlier results (7, 8), suggests that the length of stay is still substantially longer than that of non aggressive patients. Furthermore, taking into account potential side effects and the sparse evidence for effectiveness

of the pharmacological management of aggression (9), these findings cast doubt on the pharmacological interventions that are currently used in clinical practice for aggressive patients. This brings us to a final explanation for the increased number of changes amongst aggressive patients: irrational drug therapy, i.e. drugs are used whereas "there is little likelihood that it will have a beneficial effect" (10). In literature several factors contributing to irrational prescribing have been described (10-12). Amongst these, following might have increased drug prescribing in our study: the seductiveness of drugs (drugs appear more effective than they are), prescriber's fear (of the unstable condition of the patient, but also to withdraw drugs when no effect is observed), drugs can be a relatively easy way out when staff feel powerless and finally, the patient self being sometimes keen on medication, especially benzodiazepines.

Aggression was not associated with an increase in changes of somatic medication. Somatic medication is not likely to be used for the management of aggression. However, in our previous study investigating the use of as-needed medication, we did find that aggression is also associated with an increased use of as-needed somatic medication - namely analgesics like acetaminophen (5). In that study we hypothesized that this increased use could be a manifestation of demanding behaviour, as aggression is associated with demanding behaviour (13). As in this hospital analgesics are administrated predominantly on as-needed basis, it still would be interesting to investigate the use of somatic medication, especially analgesics in a studypopulation where analgesics are usually administered on regular basis.

This study has a number of methodological limitations. The current patient sample was rather heterogeneous and may not reflect daily clinical practice of more general psychiatric admission wards. The diagnoses of the subjects included psychotic and mood disorders, as well as ADHD and disruptive behaviour disorders. One might ask if changes in regular medication regimens for those disorders can be analyzed together, as pharmacotherapeutical treatment strategies are different. On the other hand in a stratified analysis for the different wards, although not significant, results in the same directions were found (data not shown). We hypothesized that aggressive behaviour is a strong determinant, influencing medication patterns across the psychiatric diagnoses. A second limitation is that while we used a validated quantitative, incident based aggression-scale, for the registration of aggression we still may have missed aggressive incidents (14). The use of a periodically administered aggression scale, like the OAS (15) might have reduced underreporting, but would have provided fewer possibilities to study temporal associations between aggression and medication changes. Furthermore, the study period seems to have been long enough to reduce the problem of underreporting.

Conclusion

In conclusion, our study reveals that for patients displaying aggressive behaviour, many changes in regular medication regimens occur. This is in line with other studies showing that changes in pharmacotherapy indicate trouble, such as comorbidity, adverse events, therapy-resistance and exacerbation of disease (e.g. 1,16,17) and, as was the case in the current study, with challenging behaviour such as aggression. Future research should unravel the reasons why regular medication regimens of aggressive patients are frequently subject to change, by focusing on the (rationality of the) decision making process associated with these changes.

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Chapter 3.3

Aggression of psychiatric patients associated with the use of as-needed medication

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Abstract

Objective Previous studies showed that aggression is an important reason to prescribe as-needed medication. The objective of this study was to compare the use of as-needed medication in aggressive and non-aggressive psychiatric patients and to explore patterns of administration of as-needed medication around aggressive incidents.

Methods An observational study in three psychiatric wards was conducted. Incidence densities of as-needed medication were determined for aggressive and non-aggressive patients and expressed as incidence density ratios (IDRs). Intensity of as-needed medication used before and following aggressive incidents was determined within a 48-hours time-window.

Results Aggressive patients had an increased use of both psychotropic and somatic as-needed medication (IDR, 2.5; 95% CI, 2.2 - 2.7 and IDR, 2.1; 95% CI, 1.8 - 2.4, respectively). Of the psychotropic medication for aggressive patients, 15% was administered in a time-window of 48 hours around an aggressive incident; in this time-window more as-needed medication was administered following an aggressive incident compared to earlier treatments.

Conclusion An increased use of both psychotropic and somatic as-needed medication is associated with aggressive behaviour. Psychotropic as-needed medication is more frequently administered shortly after an aggressive incident than shortly before. However, more often as-needed medication is administered outside the 48 hours time-window around an aggressive incident.

Introduction

Aggression by psychiatric patients has a large impact on well-being of patients and staff and is associated with high costs (1). The incidence of aggressive incidents reported in different studies ranges from 0.4 to 59.9 incidents per patient-year, depending upon the type of ward and country in which the study was conducted (2). To manage aggression, several intervention strategies are currently used, including pharmacotherapy, physical restraint and seclusion. Increased use of psychotropics by aggressive patients has been observed in observational studies. Higher dosages of psychotropics and polypharmacy are more common for aggressive patients than non-aggressive patients (3, 4). However, evidence for the effectiveness of pharmacological management of aggression is scarce (5). Psychotropics generally are prescribed in a fixed dose regimen, but as-needed regimens for the management of aggression and aggression-related symptoms like agitation and disruptive behaviour are also used (6-8) giving nursing staff greater freedom in administering medication, allowing them to administer rapidly in acute situations or at the patient's request (9). Especially antihistamines, antipsychotics and benzodiazepines are frequently used on an as-needed basis (3). Although prescription of as-needed medication appears to be widespread in psychiatry, evidence for effectiveness is lacking (9, 10). We are unaware of clinical trials that specifically looked at the efficacy of as-needed regimens in adult psychiatry, and even descriptive and more exploratory studies about current practices of as-needed regimens are scarce.

Our study aims to investigate whether aggressive psychiatric patients have an increased use of as-needed medication, compared to non-aggressive patients. In addition, this study investigates the time-relationship between the occurrence of aggressive incidents and the administration of as-needed medication in this patient group.

Methods

Setting, design and subjects

A prospective observational study was conducted in three different psychiatric wards, located in the centre of the Netherlands. All patients, hospitalized for at least two weeks during the study-period of September 2004 until May 2005, were included. All the three participating wards were long-stay wards specialized in disruptive behaviour, i.e., a forensic ward, a centre for patients with mild learning disabilities and disruptive behaviour, and an orthopsychiatric ward.

The study protocol was approved by the Scientific Committee and the Board of the hospital. Patients were informed about the study and patients were not included in case of objection to participation in the study.

Data collection

Patient characteristics were collected from the hospital database. This database contains information about demographics, DSM-IV diagnoses at admission as established by psychiatrists of the ward, compulsory hospitalization and their history of earlier admissions. When information in the patient administration database was incomplete, additional data were collected from the medical records.

Aggressive behaviour was assessed by using the Staff Observation Aggression Scale-Revised (SOAS-R), a validated aggression measurement instrument (11). This scale measures the frequency, nature, and severity of both outwardly and inwardly directed aggressive behaviour. SOAS-R scores range from 0 (no aggression) up to 22 (extremely severe aggression). For this study only outwardly directed aggressive incidents were analyzed, i.e., all forms of self-harming and suicidal behaviour were excluded.

Patients were categorized as aggressive if one or more aggressive incidents were recorded on the SOAS-R during the study period. Furthermore, aggressive patients were sub-classified as being mildly or severely aggressive. A patient was defined as being severely aggressive in case he or she was involved in one or more episodes of physical aggression towards person(s). In case a patient had exclusively displayed verbal aggression and/or aggression towards objects he or she was categorized as being mildly aggressive. If two aggressive incidents of one patient occurred within one hour, they were regarded as one incident.

As-needed medication was defined as medication which was not administered on a regular basis, but on the patient's or nurse's initiative. Hospital policy requires ward personnel to register all administrations of as-needed medications to every individual patient on standard forms. Patient name, drug name, date, time and dosage were registered. The pharmacy database was used to obtain additional information about the medication the patients received as part of their regular treatment regimens.

Outcome

Firstly, we aimed to investigate whether aggressive patients have an increased use of as-needed medication compared to non-aggressive patients. The primary outcome of this research question was the incidence density (ID) of psychotropic as-needed medication administrations for aggressive and non-aggressive patients. The ID was calculated by dividing the sum of administrated as-needed medications in one group by the total duration of follow-up in that group. The IDs for aggressive and non-aggressive patients were compared and expressed as an Incidence Density Ratio (IDR). Selected psychotropic drugs included benzodiazepines, antipsychotics and promethazine. Secondary outcome was the ID of somatic as-needed medication administrations, e.g., analgesics like acetaminophen and ibuprofen.

The second aim of this study was to investigate the temporal association between the occurrence of aggressive incidents and the administration of psychotropic as-needed medication. Outcome for this research study was the intensity of psychotropic as-needed medication use – i.e., the number of as-needed medications in a defined interval of time divided by the total number of aggressive incidents – for different time-windows before and following aggressive incidents. To avoid overlap of the time-windows around consecutive aggressive incidents, only aggressive incidents with a preceding 24-hours incident free period were included.

Analysis

Between-group characteristics were analyzed using the chi-square for categorical variables and the Mann – Whitney U test for continuous, skewed variables.
For the comparison of the incidence densities between aggressive and non-aggressive patients, incidence density ratios (IDRs) and their 95% CI were computed. To check the validity of this method, the use of aggressive patients compared to non-aggressive patients was also analyzed using a multiplicative intensity model (12) , a generalization of cox proportional hazards regression model.

To investigate the temporal association between the administration of psychotropic as-needed medication and the occurrence of aggressive incidents, the frequencies of as-needed medication administrations (= intensity) before and following an aggressive incident were compared. A Poisson distribution was observed for the administration, which could be analyzed using a multiplicative intensity model. Differences in intensity of use before and following aggressive incidents were expressed as intensity ratios (IR). Data were analyzed using S-PLUS 6.

Results

The initial study population was comprised of 130 patients. Three patients, however, objected to study participation and were therefore not included in the analysis. Furthermore, two patients who were hospitalized for less than two weeks were excluded. The mean follow-up was 170 days (range 14 – 273 days). Characteristics of the remaining 125 included patients are presented in Table 1.

Aggressive patients (n =76) turned out to differ significantly from non-aggressive patients (n = 49) in terms of age, ward, sex, and a diagnosis of conduct disorder. During the study period, 551 aggressive incidents caused by 76 patients, were recorded. Of these 76 patients, 61 were subclassified as severely aggressive and 15 as mildly aggressive. Characteristics of the aggressive incidents are displayed in Table 2. More, but less severe, incidents were recorded at the orthopsychiatric ward. At the centre for mildly mentally disabled patients a higher frequency and severity of aggressive incidents was observed compared to the two other wards.

Table 1 Characteristics of the study population

Characteristic	Patients with aggressive incident(s) (n=76)		Patients without aggressive incident(s) (n=49)		p value
	No.	(%)	No.	(%)	
Age (mean)	27.2 years		31.7 years		0.004
Ward					
Forensic psychiatry	25	32.9	31	63.3	0.001
Mentally disabled patients	29	38.2	14	28.6	
Orthopsychiatry	22	28.9	4	8.2	
Male sex	54	71.1	43	87.8	0.03
Mean duration of follow up (days)	181.4		157.1		0.28
Involuntary admission (mean percentage of total follow up)	41%		42%		0.92
Diagnosis at hospital admission (DSM IV)					
Axis I					
Psychotic disorder	37	48.7	28	57.1	0.34
Schizophrenia	33	43.4	23	46.9	0.70
Alcohol dependence/ abuse	6	7.9	7	14.3	0.25
Drug dependence/ abuse	18	23.7	13	26.5	0.72
Mood disorder	5	6.6	4	8.2	0.74
Development disorder	11	14.5	0	0	0.01
More than one Axis I diagnosis	22	28.9	14	28.6	0.96
Axis II					
Personality disorder	12	15.8	13	26.5	0.14
Cluster B	9	11.8	6	12.2	0.95
Mental retardation	30	39.5	13	26.5	0.14
Regular medication users at inclusion					
Antipsychotics	37	48.7	30	61.2	0.17
Antidepressants	15	19.7	8	16.3	0.63
Anticonvulsants	6	7.9	3	6.1	0.71
Benzodiazepines	25	32.9	16	32.7	0.98
Promethazine	2	2.6	2	4.1	0.65
Polypharmacy**	53	69.7	34	69.4	0.97
Somatic medication	23	30.3	18	36.7	0.45

***The χ^2 test was used for categorical variables and the Mann-Whitney U test for the non-parametric variables. **More than one regular psychothropic drug prescribed.**

In the nine-month of study period, 4,427 as-needed medications were administered to 44 (60%) aggressive and 20 (41%) non-aggressive patients. The most frequently administered types of psychotropic medications (n = 2940) were benzodiazepines (96.1 %) -predominantly oxazepam, diazepam, and temazepam- fol-

Table 2 Characteristics of the aggressive incidents

Ward	Incidents per bed per year		Score		Only verbal aggression	Victim of the aggressive incident needs treatment
	Mean	SD	Mean	SD	(%)	(%)
Forensic psychiatry	6.0	0.4	9.2	4.6	42.3	1.2
Mentally disabled patients	10.6	0.7	11.0	4.3	31.6	4.2
Orthopsychiatry	14.7	1.2	6.9	4.0	42.0	1.1
Total	**9.1**	**0.4**	**9.1**	**4.6**	**37.8**	**2.3**

***SOAS-R scores range from 0 to 22.**

lowed by promethazine (3.0%), and antipsychotics (0.9%). Psychotropic as-needed medication was most frequently administered orally (96.1%). In the time-window of 48 hours around the aggressive incidents, 15% of the psychotropic as-needed medication was administered. Main reasons for administration of psychotropics were comprised of "patient's demand" (53%), distress (16.6%), and sleep (13.7 %) for non-aggressive patients, and distress (36.6%), sleep (17.3%), patient's demand (16.6 %), and restlessness (13.1 %) for aggressive patients. Acetaminophen was the most frequently administered somatic as-needed medication (72.2%), followed by ibuprofen (16.1%). Main reasons for administration of somatic as-needed medication were comprised of headache (33.3%), other somatic problems (23.7 %), pain other than headache (22.1%), and patient's demand (14.9%) for non-aggressive patients, and headache (45.9%), pain other than headache (39.8%), and patient's demand (5.4%) for aggressive patients.

Use of as-needed medication in aggressive vs. non-aggressive patients

The ID for the use of psychotropic as-needed medication in aggressive patients was 5.2 administrations per person-month compared to 2.1 administrations per person-month for non-aggressive patients, corresponding to an IDR of 2.4 (95% confidence interval [CI] 2.2 - 2.7). In the multiplicative intensity model these results appeared to be valid. For oxazepam, which was administered most frequently to both aggressive and non- aggressive patients, the highest IDR was observed (IDR, 6.9; 95%CI 5.6 - 8.5).

The same analysis was performed for the use of somatic as- needed medication, resulting in IDs for aggressive patients and non-aggressive patients of 2.1 and 1.0 per person-month, respectively. The IDR was 2.1 (95% CI 1.8 - 2.4). The observed increased use of as-needed medication for aggressive patients was higher for severely aggressive patients compared to mildly aggressive patients, except for diazepam. (Table 3).

Table 3 The use of as-needed medication of non-aggressive, mildly and severely aggressive patient

As-needed medication	Patients without aggressive incident(s) (n=49)			Patients with mild aggressive incident(s) (n=15)				Patients with severe aggressive incident(s) (n=61)				
	Users		ID*	Users		ID*	IDR**	95%CI	Users		ID*	IDR**	95%CI
	N	%		N	%				N	%			
Psychotropic	20	41	2.1	7	47	3.3	1.6	1.4-1.8	37	61	5.8	2.7	2.5-3.0
Oxazepam	13	27	0.4	4	27	1.1	2.9	2.2-3.8	26	43	3.0	8.1	6.6-10.0
Diazepam	5	10	0.9	1	7	1.2	1.4	1.1-1.7	10	16	1.2	1.3	1.1-1.6
Temazepam	10	20	0.6	4	27	0.6	0.9	0.7-1.3	11	18	0.8	1.2	1.0-1.5
Other	4	8	0.2	3	20	0.4	1.7	1.1-2.6	15	25	0.8	3.6	2.7-4.8
Somatic	22	45	1.0	13	87	1.6	1.7	1.4-2.0	43	70	2.2	2.2	1.9-2.5

***Incidence density per person-month. **Incidence density ratio; reference-group is the group of patients without aggressive incidents.**

Stratified analyses for the three different wards for psychotropics and somatic as-needed medication revealed statistically significant increased use of as-needed medication for the aggressive patients in all three wards.

Time relationship between as-needed medication and aggressive incidents

During the nine-month study period, 551 outward directed aggressive incidents were recorded. For 75% of the registered aggressive incidents, no as-needed medication was administered during the 48-hours time-window around the aggressive incident. For most incidents, the number of administrations before an aggressive incident equalled the number of administrations following an aggressive incident (no difference of use at 3h: 86%, 12h: 83% , 24h: 82% , 48h: 78%). Intensity of use of psychotropic as-needed medication per 3 hours periods within the 24 hours time window before and following an aggressive incident was calculated and displayed in Fig. 1. The highest intensity of as-needed medication use was observed in the three hours following an aggressive incident. Comparing the intensity of use in this period with the intensity of use in the six hours before resulted in a ratio of 3.0 (95% CI 1.3 - 6.8). More as-needed medications were administered in the 36 hours following an aggressive incident compared to the 36 hours before (intensity ratio [IR]1.4; 95% CI 1.1 - 1.8). Furthermore, the intensity of use in the three-hour period following an aggressive incident was compared with the period from 36 hours to three hours before an aggressive incident and on the other hand with the period from three hours to 36 hours following aggressive incidents (IR 3.9; 95% CI 2.0 - 7.7 and IR 1.84; 95% CI 1.2 - 2.9, respectively).

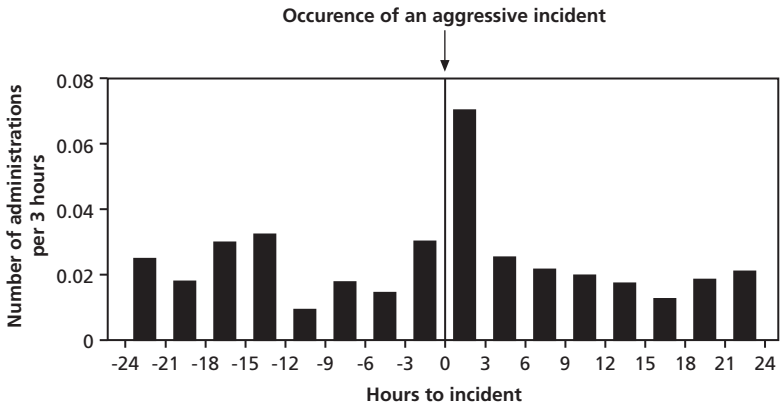

Figure 1 Intensity of as-needed medication use around aggressive incidents.

Discussion

In this observational study, conducted in three Dutch long stay wards, the association between the use of as-needed medication and aggressive behaviour was investigated. In line with previous findings that aggressive patients have an increased use of psychotropics – higher dosages and more polypharmacy (3, 4) – an increased use of psychotropic as-needed medication was observed. Interestingly, in addition to an increased use of psychotropic as-needed medication the use of somatic as-needed medication was also found to be increased. Apparently, aggressive behaviour triggers the use of as-needed medication.

Strengths of our study include the use of a validated aggression measurement instrument (the SOAS-R) and the actual use of as-needed medication as study outcome instead of the prescription of as-needed medication. Previous studies either assessed the reasons for prescription or administration of as-needed medication without the use of an aggression measurement instrument and without a group of non-aggressive patients as reference group (6-8). To our knowledge, only Soliman and Reza compared non-aggressive patients to aggressive patients (3). However, in that study, not the use of as-needed medication was analyzed, but the prescription of as-needed medication. Furthermore, in the study of Soliman and Reza, aggression was retrospectively assessed from hospital records by the researchers with the use of the SOAS-R, although the SOAS-R is designed to record aggression as soon as possible after the aggressive incident by the staff witnessing the incident.

Looking at the temporal associations between episodes of aggressive incidents and the administration of as-needed medication immediately preceding and following these aggressive incidents, an increased intensity of use was observed shortly after the aggressive incident. It seems fair to conclude that in those cases as-needed

medication is used to regain control and / or prevent further escalation. From a pharmacological point of view, the choice for oxazepam seems irrational, as the optimal effect of oxazepam is only reached after two to three hours. A better choice, to our point of view, would be lorazepam or midazolam, which have a shorter Tmax.

The interval between the administration of as-needed medication and an aggressive incident was frequently much larger than 48 hours, which suggests that aggressive behaviour leads to the administration of as-needed medication, not only immediately following aggressive incidents but also on other moments. This suggestion was reinforced by the observation that the intensity of use in the time-window of three to 36 hours following the aggressive incident was increased compared to the intensity of use in the time window of three to 36 hours before an aggressive incident. We, therefore, hypothesized that as-needed medication is not only used for the (direct) management of aggression. This hypothesis was further strengthened by the observation that not only the use of psychotropic as needed medications was increased, but also the use of somatic as-needed medications. One could think of different explanations, which could not be investigated with the available data. A plausible reason for an increased use of as-needed medication might be that the staff tends to administrate more as-needed medication to patients, once they have shown aggressive behaviour, in order to prevent future aggressive incidents. However, it might also well be possible that aggressive patients are keener on as-needed medication than non-aggressive patients and make a stronger appeal on the staff to obtain as-needed medication. Still another explanation might be that aggressive patients are more severely ill, thereby needing more medication, e.g., for insomnia.

Limitations of this study are the following. Firstly, due to the observational study-design, an association between aggression and as-needed medication could be determined, but we could not investigate the causality of this observation, i.e., is the increased use of as-needed medication caused by aggression itself or by other determinants associates with aggression? ; only hypotheses could be formulated.

Secondly, for the assessment of aggression, only the SOAS-R was used. By measuring aggression with the SOAS-R, we had to rely on staff 's willingness to report witnessed aggressive behaviour. Such measurement probably resulted in a certain degree of underreporting, especially in the case of mildly aggressive behaviour. The degree of underreporting was not assessed. However, the incidence of aggressive incidents was higher than the median incidence observed in the review of Nijman et al. (8), in which studies with aggression data, measured by the SOAS-R, were analyzed.

Furthermore, reporter-bias could have been occurred as the staff, who registered both the administration of medication and aggression, could be more willing to report an aggressive incident after administering as-needed medication. On the other hand, as the registration of as-needed medication is in practice for many years

and as around many aggressive incidents no as-needed medication was administered, the risk of such bias seems small.

Lastly, the heterogeneity of the study population might have resulted in biased risk estimation. With a dynamic study population, both chronically and newly admitted patients were included in this study, which resulted in a heterogeneous study population. With the participation of three different wards, the heterogeneity of the study population was further increased. Some heterogeneity of these three wards was reflected in the differences in severity and frequency of the aggressive incidents. Mean incidence and the percentage of victims requiring treatment, however, all fell in the range observed in the review (2). It, therefore, seemed reasonable to analyze the data of the three wards together instead of conducting stratified analyses, which would have decreased significantly the statistical power.

Taking into account our study limitations, we conclude that aggressive patients use more as-needed medication than non-aggressive patients. However, to a certain extent, the function of as-needed medication practices is unclear. As-needed medication administered immediately preceding or following the occurrence of aggressive incidents, is mainly administered to regain control and / or prevent further escalation. For the other as-needed medications administrations we can only make guesses about their function and effectiveness. A tempting hypothesis is that aggressive patients are keen on as-needed medication, which they might obtain by showing demanding behaviour. However, on the basis of this study it also might be possible that aggressive behaviour in the past leads to the administration of as-needed medication in the future, with the aim of preventing the occurrence of other aggressive incidents.

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Chapter 3.4

Beliefs of patients and nurses about as-needed medication in relation to aggression

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(submitted)

Abstract

Objective To investigate the reasons for the increased use of as-needed medication by aggressive psychiatric patients, by focusing on the beliefs of both patients and nurses about as-needed medication.

Methods Semi-structured interviews, conducted within 24 hours after an as-needed medication administration, were used to compare the beliefs of aggressive and non-aggressive patients concerning (the indications for and efficacy) of 'as-needed' medication. A sub-analysis was done for severely aggressive patients compared to non-aggressive patients.
The structured interviews were also completed by the administering nurses and their views were compared with the patient's views.

Results For severely aggressive patients, as compared to non-aggressive patients, medication was more frequently administered on the basis of the nurse's initiative (instead of the patient's initiative) (48 and 19%, respectively, $p=0.02$). Furthermore, aggressive patients more frequently perceived the dosage of the as-needed medication as high enough, compared to non-aggressive patients (65 and 35%, respectively). The perceived time of onset of medication was significantly shorter for patients as compared to nurses.

Conclusion Results show that nurses are more likely to administrate as-needed medication to aggressive patients -especially severely aggressive patients- compared to non-aggressive patients. Another important finding is that aggressive patients are more likely to receive satisfying dosages than non-aggressive patients. Combining these findings helps partially explain why aggressive patients are very likely to be exposed to as-needed medication. Overall, as- needed medication seems to fulfill both a patient's and a nurse's need.

Introduction

The use of as-needed, medication, i.e. medication administered on the nurse's initiative or patient's request, is common practice in psychiatric wards as pointed out in a recent review (1). Previous research suggests that nurses beliefs about possible indications for the use of as-needed medication strongly influence the administration of as-needed medication (2). Thus, besides doctors, nurses have a great impact on the decision-making process with regard to their administration. Moreover, the patient-nurse interaction may also influence the administration of as-needed medication, since previous studies have reported that a patient's request is a frequently mentioned reason for nurses to administer as-needed medication (1, 3, 4).

In a previous study we found that aggressive patients use more as-needed medication, compared to non-aggressive patients (3). The use of psychotropic as well as non-psychotropic (particularly non-opioid analgesics) as-needed medication use was higher amongst these patients. Furthermore, as-needed medication use by aggressive patients was also higher during aggression-free follow-up time. This possibly suggests that for aggressive patients, as-needed medication is also used for other purposes than the (direct) management of aggression. It is currently unclear what these other purposes are. Additionally, evidence indicating that as-needed regimens are effective for the treatment of behavioral disturbances (in psychotic patients) compared to regular regimens of the same drugs is lacking (5). Furthermore, there is only weak evidence for the efficacy of pharmacological treatment of aggression in general (6).

In this study, we aim to gain more insight into the reasons for the increased use of as-needed medication by aggressive psychiatric patients, by focusing on the beliefs of both patients and nurses about as-needed medication.

Methods

Setting, design and subjects

An observational follow-up study was conducted at two acute admission wards and two long-stay wards of the Altrecht Mental Health Institute in the Netherlands. The study period was January 1st 2007 - September 14th 2008. The consecutive study sample consisted of 91 patients, admitted during the study-period and using one or more as-needed medications. Patients were included if psychotropic or analgesic drugs were administered orally on an as-needed basis (the oral route being the most common for as-needed administrations (7)). These drugs included: hypnotics/sedatives (benzodiazepines and others), antipsychotics, promethazine, analgesics

(NSAIDs, opioids, and others). Anticholinergic medication was not included. No exclusion criteria were applied.

The study was approved by the Institutional Scientific Review Board, according to Dutch law. Written informed consent was obtained from patients willing to participate.

Semi-structured interviews

Patients using as-needed medication during the study period and nurses administering as-needed medication were invited to participate. A semi-structured interview was developed, in order to investigate the beliefs of both patients and nurses about the reasons for the administration and the perceived effect of used as-needed medication. To explore these topics, the following items were included in the interviews for both patients and nurses: who took the initiative for administration of the as-needed medication (i.e., the patient or a nurse), the persistence of asking for it (once, more than once), the reason for asking/giving the medication (tension, anger, fear, restlessness, pain, aggression, sleep, other), the perceived effectiveness (yes, no), time to onset of effect (<15 min, 15-60 min, 1-2 hours, >2 hours), the duration of effect (1 hour, 6 hours, 12 hours, >12 hours), frequency of administration (frequent enough, not frequent enough), and perceived strength of the administered dose (high enough, not high enough).

Furthermore, interviews with the nurses contained two additional items about the way the patient asked for the medication (calmly, agitated, friendly, pushy, or angry) and the necessity of administration as perceived by the nurse (necessary or not necessary). The interviews were pre-tested both in one of the acute wards and in one of the long-stay wards.

To reduce recall bias, patients were interviewed within 24 hours after as-needed medication was administered (LG and DM). Patients with multiple as-needed medication administrations were asked to participate only once for each different drug administered. Due to irregular shifts, nurses were allowed to complete the semi-structured interview up to 96 hours after administration.

Aggression measurement

Daily staff reports were used to assess aggressive behavior. These are reports about the behavior of individual patients. They are written during each shift by medical personnel to facilitate the transfer of information between shifts. Staff reports of a time-window from seven days before to seven days following the administration of as-needed medication were retrospectively screened for aggressive incidents. The researcher screening the staff reports (***DM***) was not aware of aggressive incidents at the time of the interview. Aggressive incidents were classified according to Hildebrand et al. (8), as verbal aggression (VA, i.e. aggressive verbalizations directed at an individual), verbal threat (VT, i.e. verbal threats or gestures that evoke fear in

staff, patients or others), or physical violence (PV, including physical force directed at both persons and objects, but excluding auto-mutilation). In the study of Hildebrand, De Ruiter et al., a good interrater reliability was observed on whether the events reported were actual aggressive incidents (Cohen's kappa =.86) (8). Patients were assigned to the aggressive group if one or more aggressive incidents were identified; patients without aggressive incidents were assigned to the non-aggressive group. Furthermore, aggressive patients were sub-classified into patients with verbal aggression (VA or VT) and physical aggression (PV). In cases of doubt about screening, consensus was reached between the main researchers (*LG, DM*).

Data analysis

Data on patient characteristics were collected from the hospital administration database and information about medication use was collected from the hospital pharmacy database.

To compare aggressive patients to non-aggressive patients, two analyses were performed: 1) all aggressive patients versus non-aggressive patients, and 2) patients with incidents of physical violence (i.e. the more severely aggressive patients) versus non-aggressive patients. Furthermore, separate analyses were performed for psychotropic and analgesic drugs. χ^2 tests (or Fisher's Exact tests when appropriate) were used for dichotomous categorical variables and Mann-Whitney U-tests for ordinal categorical variables.

To compare the answers of patients and nurses, only the data on administrations for which both patient and nurse completed the semi-structured interview were used in the analysis. McNemar tests (or Sign tests when appropriate) were used in this analysis. For all statistical tests, the criterion for significance was $p < 0.05$. All statistical analyses were carried out using SPSS v16.0 (SPSS Inc., Chicago, Illinois).

Results

Participants

In total, 91 patients were included of which 45 (49.5%) were identified as being aggressive. VA was most commonly observed, and occurred in 31 patients (74%), followed by PV in 27 patients (62%), and VT in 16 patients (38%). Aggressive behavior was also assessed for 12 patients that could not be interviewed. Of these 12 patients, eight (67%) were scored as aggressive, compared to 46% in the included population. Patient characteristics of aggressive and non-aggressive patients are shown in Table 1.

A significantly higher proportion of patients in the aggressive group had a diagnosis consistent with a form of psychotic disorder (OR: 2.7, $p = 0.03$).

Table 1 Patient characteristics of aggressive and non-aggressive patients

Demographic data	Patients with aggressive incidents (n = 45)		Patients without aggressive incidents (n = 46)		p value[a]
Age (median)	34.0	-	38.4	-	0.08
Gender male	27	60.0	29	63.0%	0.80
Diagnoses at admission					
Axis I					
Psychotic disorder	22	48.9	12	26.1	0.03*
Schizophrenia	11	24.4	5	10.9	0.09
Autistic	3	6.7	2	4.3	0.70
Mood disorder	7	15.2	4	8.9	0.40
Alcohol abuse	6	13.0	5	11.1	0.78
Drug abuse	10	22.2	15	32.6	0.27
AD(H)D	4	8.9	3	6.5	0.71
Anxiety disorder	0	0.0	2	4.3	0.50
Somatoform disorder	1	2.2	1	2.2	1.00
Dementia	1	2.2	1	2.2	1.00
Adjustment	1	2.2	2	4.3	1.00
Axis II					
Personality disorder NOS	7	15.6	6	13.0	0.73
Cluster B personality disorder	5	11.1	8	17.4	0.39
Mental retardation	13	28.9	8	17.4	0.20
Hospitalization data					
Length ward stay (median (range))[b]	27	(0 – 752)	60	(0 –981)	0.54

a For categorical variables, $\chi 2$ test was used when appropriate, otherwise Fisher's Exact test was used. For continuous skewed variables Mann-Whitney U-test was used.
b Time between admission to hospital and administration of as-needed medication.
* statistically significant, $p < 0.05$

The patients completed a total of 108 semi-structured interviews. Nurses filled in a total of 77 semi-structured interviews (response rate: 71%). Of these interviews, 65 were complementary to patient semi-structured interviews, whereas 12 interviews concerned patients who either refused to participate, were not able to participate (for instance because of seclusion), or about whom the nurse strongly advised not to invite the patient for participation (for safety reasons or for the benefit of the patient).

The semi-structured interviews involved, in descending rate of occurrence, the administration of benzodiazepines (N=64; 59.3%: oxazepam, temazepam, diazepam, lorazepam, clonazepam, clorazepate), analgesics (N=39; 36.1%: acetaminophen, ibuprofen, acetaminophen/codeine, tramadol), antihistamines (N=3; 2.8%: promethazine), hypnotics (N=1; 0.9%, zopiclon), and antipsychotics (N=1; 0.9%, zuclopenthixol).

Aggressive versus non-aggressive patients

The interviews of all non-aggressive patients were compared with all aggressive patients and physically aggressive patients only. Results of these analyses, for psychotropic and analgesic as-needed medication, are shown in Table 2.
Aggressive patients did not differ with regard to DDD-equivalent dosage (for both psychotropic and non-psychotropic drugs, data not shown). Although not statistically significant, physically aggressive patients received higher DDD compared to non-aggressive patients (median 0.29 and 0.50, respectively; p= 0.08).

Overall 88 (81%) of the as-needed medications were administered at the request of the patient, which was more frequently the case for analgesic medication (N=37; 95%) than for psychotropics (N = 88; 74%) (Fisher's Exact test, p = 0.01). Furthermore, the overall analysis showed a significantly increased initiative by the nurses to administer as-needed medication to aggressive patients, compared to non-aggressive patients for all medication (p = 0.05). When physically violent patients (n = 27) were compared with non-aggressive patients (n = 46), it was observed that physically violent patients were significantly more likely to be administered both "any" and psychotropic as-needed medication on the nurse's initiative than non-aggressive patients (OR= 4.6; p = 0.01 and OR = 6.9; p= 0.009, respectively). Moreover, also within the aggressive group, physically violent patients were significantly more likely to be administered as-needed medication on the nurse's initiative (OR 5.4; p= 0.03).

Patients' views on indications for administration of their as-needed medication did not significantly differ between aggressive and non-aggressive patients. However, aggressive patients were more likely to agree that the dosage of their as-needed medication was high enough compared to non-aggressive patients (OR: 2.36, p=0.04). This difference remained statistically significant for psychotropic drugs (OR: 3.0, p=0.04), but not for analgesics (Fisher's Exact test, OR 2.6 p = 0.47).

Differences were observed in nurses´ views on the way aggressive and non-aggressive patients asked for their medication. Aggressive patients were less likely to be regarded as asking in a friendly way for their as-needed medication compared to non-aggressive patients (OR: 0.29, p=0.02). Also, there was a trend towards aggressive patients more often being demanding (OR: 7.13, p = 0.06). When patients with incidents of physical violence (n = 13) were compared with non-aggressive patients (n = 31), nurses perceived physically aggressive patients to be significantly more demanding in asking for their medication (OR: 10.00, Fisher Exact test, p = 0.02). With regard to the reasons for administration of psychotropic drugs, nurses reported restlessness as a reason significantly more often when patients with incidents of physical aggression were involved, as compared to non-aggressive patients (OR= 6.18, p=0.001).

Table 2 Comparative answers of aggressive and non-aggressive patients

Patient questions Answers		Non-aggressive patients (n interviews = 54)		Aggressive patients (VA, VT) (n interviews = 21)	
		N	%	N	%
Initiative	Patient	48	88.9	19	90.5
	Nurse	6	11.1	2	9.5
Amount of asking	Once	44	91.7	18	94.7
	More than once	4	8.3	1	5.3
Indication[c]	Tension	5	9.3	2	9.5
	Anger	3	5.6	0	0.0
	Fear	1	1.9	2	9.5
	Restlessness	10	16.7	2	9.5
	Pain	22	40.7	5	23.8
	Aggression	0	0.0	1	4.8
	Sleep	10	18.5	7	33.3
	Other	4	7.4	3	14.3
Effectiveness	Effective	45	83.3	17	81.0
	Not effective	9	16.7	4	19.0
Time to onset	< 15 min	11	26.2	5	27.8
	15-60 min	28	66.7	10	55.6
	1-2 hours	3	7.1	3	16.7
	>2 hours	0	0.0	0	0.0
Duration of effect	1 hour	8	21.1	1	6.2
	6 hours	16	42.1	8	50.0
	12 hours	12	31.6	4	25.0
	>12 hours	2	5.3	3	18.8
Frequency of dosing	Enough	30	57.7	15	71.4
	Not enough	22	42.3	6	28.6
Strength of dose	High enough	23	45.1	14	70.0
	Not high enough	28	54.9	6	30.0
Nurse questions	**Answers**	**Non-aggressive patients (n interviews = 39)**		**Aggressive patients (VA, VT) (n interviews = 13)**	
Way of asking	Calm	25	64.1	8	61.5
	Friendly	17	43.6	4	30.8
	Demanding	1	2.6	1	7.7
	Agitated	2	5.1	0	0.0
	Angry	0	0.0	0	0.0
Necessity of medication	Yes	26	81.2	5	71.4
	No	6	18.8	2	28.6

Abbreviations: VA = verbal aggression; VT = verbal threat; PV = physical violence
For categorical variables, χ^2 test was used when appropriate, otherwise Fisher's Exact test was used.
Time to onset and duration of effect were analyzed using Mann-Whitney U-test.

Outcome measures: patients versus nurses

For 65 interviews completed by patients a matching interview completed by a nurse was available. The matched pairs concerned 55 patients of which 27 were scored

Aggressive patients (PV) (n interviews = 33)		p value[a]	p value[b]
N	%		
21	63.6	0.05*	0.01*
12	36.4		
21	100.0	0.24	0.31
0	0.0		
3	9.1	1.00	1.00
0	0.0	0.62	1.00
3	9.1	0.21	0.15
8	24.2	0.81	0.42
9	27.3	0.10	0.25
0	0.0	1.00	NA
4	12.1	1.00	0.24
6	18.2	0.25	0.32
29	87.9	0.17	0.15
4	12.1		
12	48.0	0.34	0.19
12	48.0		
1	4.0		
0	0.0		
1	4.5	0.06	0.09
15	68.2		
3	13.6		
2	13.6		
20	60.6	0.45	0.79
13	39.4		
19	63.3	0.04*	0.17
11	36.7		
Aggressive patients (PV) (n interviews = 24)			
12	54.2	0.58	0.43
3	12.5	0.02*	0.01*
5	20.8	0.06	0.03
0	0.0	0.49	0.52
0	0.0	-	-
15	100.0	0.45	0.16
0	0.0		

a Aggressive patients compared to non-aggressive patients.
b Aggressive patients with incidents of physical violence (PV) compared to non-aggressive patients.
c Total number of indications mentioned is more than 100% because more than 1 indication could be mentioned.
*** statistically significant, p < 0.05**
**** statistically significant, p < 0.01**

as aggressive (49%) and 28 as non-aggressive (51%). The main results are displayed in table 3. Nurses tended to ascribe, more often than the patients, the reasons for

Table 3 Comparative answers of patients and nurses

Question	Answer	n total	Patient answers		Nurse answers		p value[a]
			n	%	n	%	
Initiative	Patient	65	56	86.2	54	83.1	0.625
	Nurse		9	13.8	11	16.9	
Amount of asking	Once	53	51	96.2	49	92.5	0.687
	More than once		2	3.8	4	7.5	
Indication	Tension	65[b]	8	12.3	19	29.2	0.003**
	Anger		2	3.1	2	3.1	1.000
	Fear		3	4.6	4	6.2	1.000
	Restlessness		11	16.9	26	40.0	0.001**
	Pain		22	33.8	25	38.5	0.250
	headache		8	57.1	10	66.7	0.500
	other		7	42.9	5	33.3	
	Aggression		1	1.5	1	1.5	1.000
	Sleep		14	21.5	5	7.7	0.004**
	Other		9	13.8	3	4.6	0.109
Effectiveness	Effective	59	52	88.1	51	86.4	1.000
	Not Effective		7	11.9	8	13.6	
Reported effect	Effect = Indication	42	39	92.9	28	66.7	0.021*
	Effect ≠ Indication		3	7.1	14	33.3	
Time to onset	< 15 min	33	13	39.4	2	6.1	0.003**
	15-60 min		17	51.5	26	78.8	
	1-2 hours		3	9.1	4	12.1	
	>2 hours		0	0.0	1	3.0	
Frequency of dosing	Frequent enough	58	35	60.3	51	87.9	0.001**
	Not freq. enough		23	39.7	7	12.1	

a McNemar test when appropriate, Sign test was used when the cumulative marginal frequencies were lower than 20. Time to onset and duration of effect were analyzed using Wilcoxon signed-ranks test.
b Total number of indications mentioned is more than 100% because more than 1 indication could be mentioned.
*** statistically significant, p < 0.05**
**** statistically significant, p < 0.01**

administering psychotropic as-needed medication to tension (Sign test, $p = 0.003$) and restlessness (Sign test, $p = 0.001$). In contrast, patients significantly more often named sleep (Sign test, $p = 0.004$) and 'other reasons' (n.s.), which included: suicidal ideation, strengthening the sedative effect of another as-needed drug, and sadness.

In all cases where patient or nurse answered that the medication had an effect (n = 42), the reported reason for administration was compared with the reported effect. The effect reported by patients was highly concordant with the indication for administration that they reported (92.9%). For nurses in 14 cases (66.7%) the reported effect was not concordant with the indication, which was significantly more as compared to the concordance for patients (Sign test, $p = 0.02$). In 13 of these 14 cases the reported answers showed that the effect was a decrease of contact between patient and nurse, e.g. ´the patient did not ask for medication anymore´ or ´patient did not come back with complaints about symptoms´ or 'went to sleep'. Furthermore, nurses reported four times (9%) that they could not answer the question about the effect for reasons such as 'off-duty quickly after administration' or 'did not observe the patient after administration because patient went to bed'.

With regard to time to onset of effect, patients reported an effect to start significantly earlier than the nurses did ($T = 15$, $p = 0.003$, $r = -0.37$). This difference remained statistically significant for psychotropics ($n = 42$, $T = 5$, $p = 0.01$), and a trend was observed for analgesics ($n = 24$, $T = 3$, $p = 0.01$). Duration of effect was not perceived as being significantly different in both groups. When patients and nurses were asked if the as-needed medication could be administered frequently enough, i.e. as prescribed by the doctor's prescription, nurses tended to agree significantly more often with the fact that administration was frequent enough compared to patients (88% vs. 60%, Sign test, $p = 0.001$). This was observed especially for psychotropic drugs; nurses agreed that administration was frequent enough in 94.4% of the cases, compared to 58.3% of the patients (Sign test, $p = 0.001$). Interestingly, a rather high proportion of both patients and nurses (47% and 39%, respectively, n.s.) reported that the dosage was not high enough.

Discussion

In this study we focused on beliefs of patients and nurses about the administration of as-needed medication to aggressive and non-aggressive patients. The results emphasize the importance of the patient him or herself in the administration of as-needed medication, since in the majority of cases (almost 85%) the medication was administered on the patient's initiative. Additionally, we found that the interviewed patients rarely had to ask more than once for the as-needed medication to get it. Although we did not record how often patients' requests were rejected, these results further indicate that prescribed as-needed medication is easily obtained by patients when asking for it. A credible conclusion of this study is that patients are keen on as-needed medication, predominantly benzodiazepines. This hypothesis is further supported by the observation that more than one-third of all patients in

both groups answered they would like to receive their as-needed medication more frequently than prescribed.

Initiative by the nurse to administer as-needed medication was more frequently observed with severely (physically) aggressive patients. The increased initiative of nurses in administrating as-needed medication -in addition to the previously presumed keenness of patients on as-needed medication- is an answer our research question, aimed at finding a reason for the increased use of as-needed medication by aggressive patients compared to non-aggressive patients (3, 9, 10). The observation that aggressive patients were significantly more likely to be satisfied with their (high) dosage is also an indication that nurses are more likely to give satisfying amounts of as-needed medication to aggressive patients.

Combining this willingness of caretakers to administer as-needed medication to (physically) aggressive patients with the keenness of patients in general on as-needed medication, leads to the following vicious circle risk hypothesis: (physical) violence leads to the administration of more as-needed medication, in this study mainly benzodiazepines. Patients are satisfied with this practice which thus sustains the occurrence of aggression. Comparing patients' and nurses' views about as-needed drug administrations, shows patients' perceived time to onset of medication-effect to be significantly shorter than that of the nurses. 40% of the patients reported time to onset to be within the first 15 minutes, which is likely to be a placebo-effect. Another noticeable observation is that whereas patients named sleep disturbance as a reason for more than 30% of the administrations, nurses reported sleep disturbance in only 12% of the cases. This is in line with McKenzie et al. (11), who found that, while temazepam (predominantly given during the night shift) accounted for 27.8% of total administrations, sleep disturbance was only given as a reason by the nurses in 5.8% of the administrations.

The strength of our study is that we obtained information from both patients and nurses on their beliefs about as-needed medications directly, concerning the same administration, in contrast with previous studies using (retrospective) chart reports. The current study also has some limitations. Firstly, the fact that both newly admitted patients and more chronic patients were included, as well as patients from different wards, resulted in a heterogeneous sample, which may have affected our results. Lastly, one might speculate whether the results obtained in this study are generalizable to settings in other countries. Whereas a recent review shows that typical antipsychotics are frequently used as as-needed medication (10-100% of all administrations) (1), in our study antipsychotics only accounted for 0.9 % of all administrations. On the other hand, the kind of drug used might not be so important when assuming that as-needed practices is more about needs of patients and nurses and that the effect is (partly) placebo instead of a pharmacological one.

From an evidence-based point of view, benzodiazepines administered as as-needed medication are likely to be effective for sleep disturbances. However, less

evidence is available for vague complaints like tension and restlessness and therefore the use of as needed medication for these reasons, might be less advisable. On the other hand, results of this study show that as-needed medication fulfills both patients' and nurses' needs. It is quite plausible to conclude therefore that reducing as-needed medication practices will result in an increased use of regular medication. Moreover, a switch from as-needed medication to regular medication is likely to result in an overall increase of psychotropic use, as supported by the results of pain studies where more analgesics are used if they are administered on a regular as compared to an as-needed basis (12). Furthermore, it is questionable whether the perceived efficacy of medication administered on as-needed basis will be as strong when medication is administered on regular basis, i.e. will the assumed placebo-effect be the same and as strong when administered on regular basis. This brings us to our final point, that future research should focus on unraveling the psychological function of as-needed medication, instead of (only) focusing on clinical efficacy and. By doing so, clues might be found to potential alternatives. Without alternatives for as-needed medication, attempts to cut down or regulate as-needed medication practices are likely to fail.

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Chapter 3.5

The association of aggression and medication use with treatment outcome of hospitalized psychiatric patients

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(submitted)

Abstract

Background: Aggression is a difficult to manage behaviour in psychiatric wards. Pharmacotherapy is frequently used to manage aggression, despite insufficient evidence.

Objectives: To investigate the association between both aggression and psychotropic use on the one hand, and treatment outcome of hospitalized psychiatric patients on the other.

Methods: A case-control study was conducted in three psychiatric wards. Cases were patients with a negative treatment outcome defined as a transfer to a more restrictive ward or no transfer during the study period. Controls were patients with a positive treatment outcome defined as a transfer to a less restrictive ward. Logistic regression was used to estimate the strength of the association of aggression and the use of medication with the outcome, and expressed as odds ratios (adjusted for age, gender and diagnosis).

Results: A total of 48 (36.4%) patients of the 132 included patients had a negative treatment outcome, 84 (63.6%) had a positive treatment outcome. Patients were divided in four subgroups: not aggressive and without psychotropic polypharmacy (N=31), not aggressive and with psychotropic polypharmacy (N=15), aggressive and without psychotropic polypharmacy (N=50), and aggressive with psychotropic polypharmacy (N=36). Aggressive patients using psychotropic polypharmacy were at highest risk for a negative treatment outcome (Odds ratio 7.6; 95%CI 2.0-29.9; reference = patients without aggression, without polypharmacy)

Conclusion: Aggressive patients are at higher risk for a negative treatment outcome, especially those using psychotropic polypharmacy. As psychotropic polypharmacy does not seem to positively influence treatment outcome and considering the lack of evidence for the pharmacological management of aggression, cautiousness is recommended for the pharmacological management of aggression.

Introduction

Aggression is a difficult to manage behaviour, which is frequently observed on psychiatric wards (1). Inpatient aggression not only negatively influences the safety and wellbeing of staff and patients, but also the length of stay (2-4). Empirical research has also shown that aggression is associated with increased use of psychotropics, both in the acute situation and for the ongoing management of aggression (1, 5, 6). For the maintenance management of aggression, an increased use of psychotropics can hardly be justified given the lack of evidence (7). The fact that clinicians try to manage difficult behaviour with psychotropic drugs, while empirical evidence is scarce, might be the high impact of aggressive behaviour pressuring to act, combined with clinical experience that medication for some patients can reduce aggressive behaviour. However, it remains unclear whether the use of psychotropics for aggressive behaviour indeed positively influences treatment in daily clinical practice. Ideally, such a question is answered by conducting randomized controlled trials (RCTs) -which are considered gold standard to obtain evidence. Previous research, however, suggests that such trials are difficult to conduct, because aggressive patients of clinical are difficult to include in randomized controlled trials (RCTs) (8). Furthermore the generalizability of RCTs to clinical practice is low. In such cases, where RCTs are difficult to conduct observational research can contribute to evidence of treatment effectiveness (9).

In this study we aim to investigate the associations between both aggressive behaviour and medication on the one hand, with treatment outcome of patients admitted to psychiatric wards on the other.

Methods

Study setting, design and subjects

The setting of this observational study was the Altrecht Mental Health Care Institute. Patients admitted during the period of September 2004- November 2005 at three different wards, i.e. a forensic ward, a ward for patients with severe psychiatric disorders combined with mild learning disabilities, and a ward for juveniles with severe behavioural problems, were included. The wards have both restrictive (locked) and less restrictive (open) wards.

A minimal observation period of 30 days was required for inclusion in the present study. Excluded were those patients who both a) were not transferred to another ward or discharged during the study period, and b) were admitted for a period shorter than six months, were excluded. No other exclusion criteria were applied.

The individual patient was observed until transfer or, in case of no transfer, until the end of the study period.

Demographic, diagnostic and medication information for this study was gathered from the hospital databases and hospital records. Aggressive behaviour of the patients was measured using the Staff Observation Aggression Scale-Revised (SOAS-R) (10).

Patients were informed about the study, and were only included if they did not object to participation; two patients objected to study participation and therefore were excluded. The Scientific Committee and the Board of the mental health care centre approved the study protocol.

Outcome

Treatment outcome was classified as either negative (cases) or positive (controls) according to the level of restrictiveness of the ward to which patients were transferred. Patients were considered having a negative treatment outcome if they were transferred to a more restrictive ward, i.e. either from an open to a semi-locked or a locked ward, or from a semi-locked to a locked ward. In addition, patients who were admitted for at least six months at the same ward (i.e. without a transfer) were also defined as having a negative treatment outcome. Patients who were transferred to a ward with a lower level of restrictiveness, i.e. from a locked ward to either a semi-locked or open ward, or patients who were transferred from a semi-locked ward to an open ward, were considered to have a positive treatment outcome, as were patients who were discharged from the hospital.

Determinants

The main determinants under investigation are aggressive behaviour and the use of psychotropics. Patients were classified as aggressive if they displayed aggression on one or more occasions during the their observation time, as recorded with the SOAS-R (10) were classified as aggressive patients. Patients without such aggressive incidents were categorized as being non-aggressive.

For the use of psychotropics we determined for every patient whether or not they were using anxiolytics, hypnotics, antidepressants, antipsychotics or moodstabilizers at the time of treatment outcome. Subsequently the total number of different psychotropics used at time of treatment outcome was calculated.

Furthermore, other patient characteristics including age, gender and DSM-IV diagnosis were collected, as these were considered as potential confounders.

Data analysis

A logistic regression model was used to estimate the strength of the association between the determinants under investigation and the outcome and expressed as odds ratios (OR) (adjusted for age, gender and diagnosis).

Table 1 Patient characteristics

	Negative treatment outcome (N=48)		Positive treatment outcome (N=84)		p value
	N	%	N	%	
Aggressive	36	75.0	50	59.5	0.07
Sex, male	38	79.2	57	67.9	0.16
Age (median)	33		23		0.00
DSM IV diagnosis					
Substance	17	35.4	18	21.4	0.08
Drugs	14	29.2	18	21.4	0.32
Alcohol	5	10.4	6	7.1	0.53
Psychotic disorder	34	70.8	40	52.4	0.01
Schizophrenia	26	54.2	24	28.6	0.01
Mooddisorder	1	2.1	13	15.5	0.02
ADHD & disruptive behaviour	1	2.1	19	22.6	0.002
Autism	2	4.2	12	14.3	0.07
Personality disorder	16	33.3	9	10.7	0.001
Cluster B	9	18.8	6	7.1	0.04
NOS	7	14.6	3	3.6	0.04
Mental retardation	16	33.3	31	36.9	0.68
Medication					
Use of =>2 psychotropics	24	50.0	27	32.1	0.04
Antipsychotics use	26	54.2	39	46.4	0.40
Benzodiazepines use	20	41.7	13	15.5	0.001
Antidepressants use	12	25.0	13	15.5	0.18
Moodstabilizers, yes	5	10.4	3	3.6	0.14
Medication changes 1 month prior to event , yes	8	16.7	15	17.9	0.86

In the multivariate logistic regression model, determinants univariately associated with a p value of <0.2 were entered. Unadjusted as well as multivariate adjusted odds ratios and corresponding 95% confidence intervals (CI) are reported in the current paper.

Furthermore, the same analysis was used to determine the interaction of the two main determinants under investigation and their association with treatment outcome, by classifying the patients into four subgroups:

1) patients without aggressive behaviour and using less than two psychotropics;
2) patients without aggressive behaviour and using two or more psychotropics;
3) patients with aggressive behaviour and using less than two psychotropics and;
4) patients with aggressive behaviour and using two or more psychotropics.

The group of patients without aggressive behaviour and using less than two psychotropics was used as reference group.

Table 2 Association of aggression and medication with a negative treatment outcome.

	Unadjusted OR (95% CI)	Adjusted OR (95%CI)*
Aggression	2.0 (0.9-4.5)	4.4 (1.6-11.8)
Use of =>2 psychotropics	2.3 (1.1-4.9)	1.8 (0.7-4.7)
Sex, male	1.8 (0.8-4.1)	2.0 (0.6-6.3)
Age	1.1 (1.0-1.1)	1.0 (0.9-1.1)
DSM IV diagnosis		
Substance abuse	2.0 (0.9-4.4)	1.0 (0.4-2.9)
Psychotic disorder	2.7 (1.3-5.7)	1.6 (0.5-5.0)
Mooddisorder	0.1 (0.02-0.9)	0.1 (0.01-1.4)
ADHD & disruptive behaviour	0.1 (0.01-0.6)	0.1 (0.01-0.7)
Autism	0.3 (0.1-1.2)	0.5 (0.1-2.8)
Personality disorder	4.2 (1.7-10.4)	5.2 (1.5-17.9)

*** Adjusted for aggression, use psychotropics, sex, age, substance abuse/ dependency, psychotic disorder, mooddisorder, ADHD & disruptive behaviour disorder, autism, personality disorder.**

Results

Patients

In this study 132 patients met the in- and exclusion criteria. Of these patients 84 (63.6%) had a positive treatment outcome. Of the 48 (36.4%) patients with a negative treatment outcome, 18 were transferred to a ward with a higher level of restrictiveness and the remaining 30 had no outcome but stayed for six months or longer at the same ward.

Characteristics of the cases and controls are represented in Table 1. In the univariate analysis seven variables— higher age, having a psychotic disorder or personality disorder, not having a mood disorder or ADHD / a disruptive behaviour disorder, using more than one psychotropic and the use of benzodiazepines —were individually associated at the $p < 0.05$ level with an increased likelihood of having a negative treatment outcome.

In the multivariate logistic regression analysis, the following were statistically significant associated with having a negative treatment outcome: aggressive behaviour, having a personality disorder and not having ADHD/disruptive behaviour disorder (see Table 2). The variable "use of benzodiazepines", univariately associated with $p< 0.2$, was not entered in the model as this variable is part of a determinant already entered in the model, i.e. the number of psychotropics used at time of treatment outcome. For patients with aggressive behaviour an OR of 4.3 (95% CI 1.6-11.6) was observed. For the use of two or more psychotropics an OR of 2.1 (95% CI 1.02-4.3) was observed.

In a separate multivariate logistic regression analysis, where the determinants aggression and using two or more psychotropics (yes/no) were combined, aggres-

Table 3 Association of both aggression and medication with a negative treatment outcome.

	Patients without aggressive behaviour		Patients with aggressive behaviour	
	N	Unadjusted / adjusted OR (95% CI)	N	Unadjusted / adjusted OR (95% CI)
Patients using < 2 psychotropics	31	reference	50	1.4 (0.5-3.7) / 3.4 (1.0-11.8)*
Patients using 2 or more psychotropics	15	1.0 (0.3-4.2) / 1.2 (0.2-6.0)*	36	3.6 (1.3-10.2) / 7.6 (2.0-29.9)*

* Adjusted for gender, age, substance abuse/ dependency, psychotic disorder, mooddisorder, ADHD & disruptive behaviour disorder, autism, personality disorder.

sive patients using two or more psychotropics appeared to be at highest risk of having a poor treatment prognosis (i.e., being transferred to another locked ward or having to stay at the current locked ward) (OR 7.9, 95% CI 2.0-29.9) (Table 3).

Discussion

In the present study we found that especially aggression, and in a lesser extent the use of medication, is associated with a higher likelihood of having a negative treatment outcome, i.e. being transferred to a more restrictive ward or to stay for a long time (at least six months) at the same ward. The finding that aggression is strongly associated with a negative treatment outcome is in line with previous studies conducted in acute psychiatric wards (2-4), showing that aggression is a predictor of lengthy hospitalization. The question is how these results could be interpreted.

It could be for example that the patients with aggressive behaviour and polypharmacy have a more severe psychiatric disorder, like schizophrenia, thereby requiring more medication. However, in this study we adjusted for diagnoses, which implies that the observed association of aggressive behaviour and medication use with a negative treatment outcome is independent of diagnosis. What we cannot rule out is that this might have to do with the severity within the disease. A previous study showed that (psychotic) patients who are more severely ill at admission are at higher risk for polypharmacy and high dosages of medication; possibly these patients who are more severely ill are also at higher risk to have a negative treatment outcome. However, considering one of our previous studies (submitted) showing a temporal association of medication changes and aggression, we think that severity of illness might partly but certainly not fully explain our findings.

We therefore hypothesize that a subgroup of aggressive patients ends up with a high level of polypharmacy in an attempt to manage and reduce their aggressive behaviour. In this subgroup this apparently did not lead to a positive treatment out-

come, although we cannot tell whether the disruptive behaviour would not have been even more severe without the use of (multiple) psychotropics.

But if polypharmacy does not improve the treatment outcome, at least in terms of being able to go to a less restrictive living environment, then why do aggressive patients with a negative treatment outcome use more psychotropics? On the basis of our results, we hypothesize that aggression is a transnosological factor associated with a negative treatment outcome. In that case polypharmacy might reflect the need of clinicians to do something when facing aggression, as it is a behaviour known to be one of the characteristics of difficult patients (11).

Another finding further supporting that the results have to do with difficult patients, is the observation that (cluster B) personality disorder -a diagnosis considered to be a characteristic of difficult patients (11)- was also found to be strongly associated with a negative treatment outcome.

Concluding that polypharmacy is probably a proxy for difficult to treat patients, the question remains if it is adequate to enhance polypharmacy in the case of aggression, considering the paucity of available evidence for the pharmacological management of aggression (7). With regard to this, we refer to a recent pilot study of Mistler et al. (12) showing that reducing polypharmacy by using a medication-reduction algorithm, resulted in the same amount of symptom reduction as measured with the Brief Psychiatric Rating Scale, but a slightly longer, although not significant, duration of hospitalization. Further research is needed to investigate whether similar results can be observed when reducing medication use for aggressive patients.

The study also has some obvious limitations. The most important limitation is that no data about the occurrence of aggression were available from the patients admitted before the start of the study period. This means that patients might be classified incorrectly as non-aggressive, if they were aggressive before the start of the study period. This possible incorrect classification therefore might have led to an underestimation of our results. Another study limitation, which we believe to be a strength at the same time, is the heterogeneity of the study population. It can be considered as a limitation as a heterogeneous population increases the risk on confounding. On the other hand it is a strength, as in a homogeneous population we could not demonstrate the trans-nosological association of aggression and polypharmacy with a negative treatment outcome. A last limitation is the way in which treatment outcome was put into operation, i.e. as a transfer to a more or less restrictive environment. This way of defining might be too global. Patients, who for example are on a waiting list for a transfer to a less restrictive environment, could have been wrongly classified as having a negative treatment outcome. The use of scales, e.g. a quality of life scale or a clinical global impression-improvement scale (CGI-I) (13) could have prevented such misclassification.

Taking into account the study limitations, we conclude that patients showing aggressive behaviour, especially when using more than one psychotropic, are at an increased risk of having a negative treatment outcome. As polypharmacy does not seem to positively influence treatment outcome and considering the potential side effects of medication, from a clinical point of view, cautiousness is recommended when prescribing psychotropics for the management of aggression, e.g. by systematic evaluating the effect. Tapering or withdrawal should be considered in the case of no effect. This recommendation is in line with a recent study of Kleijer et al. (14). These authors found that of the patients with dementia treated with antipsychotics for behavioural problems, only one out of six patients improved, whereas in most patients behavioural problems continued to increase. Furthermore, after antipsychotic withdrawal 58% of the patients remained stable. From a broader perspective, the development of guidelines for repetitively aggressive patients, also embedding maintenance pharmacotherapy, is recommended. To our knowledge, current guidelines especially focus on the management of acute aggression and workplace safety, whereas clinical guidelines on the individual patient level are sparse.

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Chapter 4

General discussion

Introduction

In the introduction of this thesis we have outlined the impact of aggression on psychiatric care. Aggression is an important trigger for hospitalisation of psychiatric patients. Furthermore, aggressive behaviour on psychiatric wards has a severe impact on the well being of patients and staff, and leads to high costs (1). Subsequently, we reviewed the management of aggressive behaviour in psychiatric patients through the years. Roughly, it appears that the interventions used can be classified into three main categories: restricting freedom of movement (either by seclusion or mechanical restraints), the use of pharmacologically active substances, and a variety of more behavioural and interactional approaches.

Many of the interventions that have been used in the past -like prolonged bathing therapy, insulin induced coma and lobotomy- are currently highly outdated and deemed irrational when not viewed in their historical background. In the Netherlands in particular, seclusion has been, and still is, a frequently used response to inpatient aggression, (2, 3); however, the use of this measure is heavily debated and getting more and more in discredit (4). Another intervention that has been in use for a long time is the psychopharmacological approach; hyoscine and barbiturates in the past, antipsychotics and benzodiazepines in the present. In this thesis, we focused on the evidence available from clinical trials for the pharmacological management of aggressive behaviour, and juxtaposed that against clinical practice. Patterns in the use of medication by aggressive psychiatric inpatients were investigated in daily clinical practice, aiming to elucidate the reasons for, and effectiveness of, increased use of medication among aggressive patients.

What attracted attention throughout this thesis, is the lack of clarity about the concept aggressive behaviour; e.g. in the two systematic reviews (***chapter 2.1*** and ***2.2***) where it was found that numerous scales have been used to measure aggressive behaviour and in ***chapter 3.1*** in which we found underreporting of aggressive behaviour, which may be due to a lack of registration, but may also be linked to a difference in perception of what should be considered as aggression (5). Another important theme, which we encountered, is the highly reactive character of the way in which pharmacological interventions are applied in response to aggressive behaviour, which sometimes, at least at face value, seems irrational. In this general discussion we will elaborate on these two themes by combining current available knowledge with the results of the studies in this thesis.

First, we will discuss the concept of aggressive behaviour: should it be approached as (a symptom of) certain specific psychiatric diseases, or rather be viewed as a distinct difficult behavioural problem that may, or may not need treatment and how can it be measured? Subsequently, we will discuss the management of aggression in daily practice, especially the pharmacological management. Finally, we will

propose a number of strategies to make progress in the development and study of (pharmacological) interventions for the management of aggressive behaviour.

Aggressive behaviour: symptom of certain psychiatric disorders or separate trans-nosological problem behaviour?

Aggression is a very heterogeneous phenomenon; it encompasses a group of behaviours having in common that they are threatening, hostile, injurious, or destructive against persons or things. Several theories -including biological, sociological and psychological ones- exist about aggressive behaviour, of which most state that some forms of aggressive behaviour are useful (e.g. for survival) and other forms can be viewed as pathological (6-8). Clearly, what causes aggression is as heterogeneous as the various forms in which the behaviour is expressed.

In this thesis we focussed on aggressive behaviour in mental health institutes, which is also generally prevalent in society, as shown e.g. by numbers of the police statistics and victimization surveys (9). Considering both the trans-nosological character of aggressive behaviour in mental health care and the prevalence of (pathological) aggressive behaviour in community brings up the question whether aggressive behaviour should be viewed as a distinct problem, apart from the present psychiatric disorder, or if there are reasons to consider aggression as a behaviour associated with specific psychiatric disorders. And thereupon, what are the consequences for diagnostics? Should aggressive behaviour possibly be included in the DSM –V, e.g. as a main diagnosis / category, besides the already existing DSM –IV diagnoses " Intermittent explosive disorder" and diagnoses for which aggression or aggression related symptoms already are already considered a core psychopathological symptom, e.g. antisocial personality disorder and conduct disorder? Or: should aggressive behaviour perhaps be placed on a separate DSM-axis to reflect that this symptom is more of a dimensional nature and can be present in various degrees of severity in combination with a variety of the dichotomous Axis I and Axis II diagnostic categories? In the following paragraphs we will attempt to answer these questions by exploring the nature of the associations between psychiatric disorders and aggressive behaviour from several perspectives.

If there is a link between mental illness and aggressive behaviour, an increased frequency of aggressive incidents can be expected in psychiatric people with a psychiatric disorder compared to people without a psychiatric disorder. A large epidemiological study in the US does show that patients with severe mental illness –schizophrenia, bipolar disorder and major depression- were two to three times as likely to be assaultive compared to people without such an illness (10). This has been investigated thoroughly and confirmed for schizophrenia in particular by Hodgins et al. who studied a large birth cohort showing that for patients with schizophre-

nia and at least one hospitalization in a psychiatric ward, the risk of violent crime is 4.6 times higher for men and 23.2 times higher for women compared to those without an admission to a psychiatric ward (11). A recent review shows, that within the population of patients with a severe mental disorder, the lowest prevalence of violence (2.3 -11.0%) was observed among outpatients; highest prevalence was observed during the months prior to admission of inpatients, with a range of 19.2% in emergency departments to 50% for committed inpatients (12). For inpatients prevalence during hospitalization ranged from 16-23%. In our study sample of patients on wards for externalizing behaviour disorders we observed a relatively high percentage of patients displaying one or more aggressive incidents (e.g., 61% for all kinds of aggressive behaviour in the studies described in ***chapter 3.2*** and ***3.5*** and nearly 50% for physical aggressive behaviour in ***chapter 3.4***), as compared to acute psychiatric wards In a recent review the percentage of patients involved in an aggressive incident was lower than 25% in nine of the 12 included studies whereas in the three other studies this percentage ranged from 35 – 45%. Evidence for a link with aggression and schizophrenia is robust –especially in patients with untreated psychosis (13). Other studies, however, indicated that mental illness in itself does not increase the risk of aggressive behaviour, but rather the presence of (multiple) risk factors leading to aggression (14, 15). Other psychiatric disorders for which an increased risk of aggressive behaviour was observed include antisocial and borderline personality disorder, mental retardation, mania and post traumatic stress disorder, though contradictory results with regards to this association has been observed in some studies (16). Imperative hallucinations, have been mentioned to be associated with aggressive behaviour in some studies, but not in others(17). Formal thought disorder is a psychopathological symptom, consistently found to be associated with aggressive behaviour (18-20). Another disease factor increasing the risk of aggressive behaviour among psychiatric patients is acute mental illness. Supporting this association is the observation that on psychiatric wards most aggressive incidents occur within the first few days of admission (21). Furthermore, Steadman et al have shown that there is no difference in the prevalence of violence among discharged mental patients without symptoms and without substance compared to other people in their neighbourhood (22). For the studies in this thesis, we did not measure acute psychiatric illness over time, e.g. by periodically assessing GAF scores. This is a limitation of our studies, as the lack of such information hampered us to determine whether the increased number of medication changes, as described in ***chapter 3.2***, is a reaction on aggressive behaviour solely, or a contribution of the severity of the psychiatric main diagnosis as well.

From a neurobiological point of view, the neurotransmitters serotonin, GABA and dopamine are likely to play a key role in aggression modulation (23), of which serotonin has been investigated most extensively. This neurotransmitter can interact with 14 different serotonergic receptors and the regulation of its activity also

uses a very efficient 5-HT transporter system (24). Although the 5-HT 1A and 5-HT1B receptors are postulated as potential important modulators of aggression, several other serotonergic receptors can still play an important role. Dysfunction of the serotonergic function has been suggested as a factor contributing to aggressive behaviour in several mental disorders, including borderline personality disorder and ADHD. However, this is not backed by extensive research literature (25).

The previously mentioned observation that there is no difference in the prevalence of violence among discharged mental patients compared to their neighbourhood also suggests that treatment decreases the risk of aggressive behaviour and grounds the association between acute mental illness and aggressive behaviour. In line with this hypothesis are the results of the CATIE study, in which a 6-month decrease in violence was observed for medication adherent schizophrenic patients (13).

The patient characteristic univocally (26) associated with an increased risk of aggressive behaviour in all studies, is a previous history of violence (17). This factor probably contributed to the high proportion of patients displaying aggressive behaviour in our study population that consisted of patients with externalizing behaviour disorders. Evidence for the association of a history of violence with aggression on psychiatric wards is available for previous inpatient aggression, aggression prior to admission, aggression outside of institutions and aggression in the family of origin (17). Besides perpetration of violence, victimization, i.e. physical abuse throughout life, is also associated with aggressive behaviour (22). Substance abuse is another determinant strongly associated with aggressive behaviour. Substance abuse is a strong risk factor for aggressive behaviour in general community, and it seems an even higher risk factor in the population of psychiatric patients (22). Interestingly, in our study population aggressive patients were not diagnosed more frequently with substance abuse or dependency compared to non-aggressive patients (see ***chapter 3.2, 3.3 and 3.5***). The ward rules prohibiting substance use may only partly explain this observation. Although substance use is not allowed in the wards, clinical experience shows that also during admissions patients are able to obtain drugs or alcohol, be it far not as abundantly as in their home situation. An other explanation may be that in wards specialized in externalizing behaviour disorders like in our study population, where most patients have a history of violence before admission which is a predictor of future aggressive behaviour, substance abuse is not a discriminating risk factor anymore. Alternatively, there may be an underreporting of substance abuse and dependency in the hospital administration database.

Besides patient characteristics, it is well imaginable that environmental factors on psychiatric wards also influence the occurrence of aggression. However, to our knowledge, little is known about this relationship. An exception is the recent study of Bowers et al, who gathered data of 136 wards and found that high structure on a ward, for which teamwork is critical, lowers both rates of conflict -including

aggressive behaviour- and containment including coercive measures (27). Other research indicates that crowding (28) is associated with aggressive behaviour. Furthermore, one study showed that mixing wards for severely disturbed psychiatric patients with less disturbed psychiatric patients resulted in a decrease of aggressive incidents (29) This is remarkable, to our point of view, considering that the old policy is to separate patients into different wards according to the categorization of "easy" and "difficult".

Overall we conclude that there is a link between psychiatric disorders and aggressive behaviour. However this link is complex: aggressive behaviour is observed through a whole range of psychiatric disorders where increased risk of aggression in the individual patient results from multiple risk factors.

What is the consequence of the unclear status of aggression within psychiatry?

Despite a vast amount of studies investigating aggressive behaviour in mental health care, previous paragraphs show that still much needs to be elucidated about the concept of aggression.

The unclear concept hinders further progress in research, e.g. in the search of medication with anti-aggressive properties. This is illustrated by the regulatory agency, the FDA, who states that "for approval of a drug treatment for any condition, requires that the condition be identified and defined unambiguously, that appropriate instruments be used for assessment and measurement, and that appropriately designed clinical trials demonstrate safety and effectiveness" (30) . These regulations may have been one of the contributing factors that hindered further investigation into the anti-aggressive properties of eltoprazine and are probably the reason that until now just few efforts are put into the development of drugs with specific anti-aggressive properties without sedating the patient, for the maintenance treatment of aggressive behaviour.

In daily clinical practice a consequence of the unclear concept of aggressive behaviour is that in many wards no systematic attention is paid to aggression, e.g. by monitoring it. Furthermore, it seems like education about aggressive behaviour in training for psychiatrists only receives little attention, as far as we are aware of. This is quite remarkable, considering the impact, and the negative treatment outcome associated with aggression, as shown in ***chapter 3.4***.

Despite the elusiveness of the concept, we conclude that there is a strong link between the occurrence of aggression and mental illness. At the same time we realise that aggressive behaviour is something interactional and that, although less investigated, external factors, like the restrictive character on psychiatric wards, are very likely to contribute to aggressive behaviour, at least in the way it occurs. Therefore, one should be careful in labelling it as a psychiatric symptom or disease. Taking this into account, we still give an affirmative answer on the question whether aggres-

sive behaviour should be included in one way or another into the DSM-V. The first reason for this is that link between mental disorder has been shown in several studies, particularly for schizophrenia but also for several other psychiatric disorders and psychopathological symptoms. Furthermore, aggressive behaviour is associated with negative consequences for the patient, thereby deserving attention both in the way of treatment and research. Including aggressive behaviour into the DSM V as a separate entity could lead to a more systematically approach of aggressive behaviour and more awareness of and care for aggressive behaviour. With regard how to include aggressive behaviour into the DSM we believe the most appropriate way is through cross cutting assessment as proposed in the draft of DSM V, which came available for public review the tenth of February 2010. "The aim of this kind of cross cutting assessment is to provide quantitative measures of important clinical areas that will be relevant beyond any set of syndromal criteria. It is designed to be used at an initial evaluation to establish a baseline, and on follow-up visits to track changes. It does not relate to any specific disorder and does not serve as a screening test for DSM disorders" (31). Considering the trans-nosological nature of aggressive behaviour, which is influenced by multiple risk factors, we believe aggressive behaviour fits this kind of assessment.

Aggressive behaviour: measurement

The various available methods of measuring of aggression appear to reflect disagreement on the definition of aggression. Currently, numerous different tools are in use for the measurement of aggression; among these are diagnosis-related scales as well as incident-based scales. To date, in our study see ***chapter 2.2***, systematically reviewing the evidence for the pharmacological management of aggression, we counted 21 different outcome measures in the 35 evaluated randomized controlled trials. This was an important cause that in this systematic review we were unable to perform a quantitative evidence synthesis in addition to the qualitative evidence synthesis. This strongly suggests that for research, but also for clinical practice, more uniformity for the measurement of aggressive behaviour is desirable.

When aiming for uniformity in measurement, the choice for a particular scale is of paramount importance. Aggression measurement can be:

- based upon actually occurring aggressive behaviour, like the SOAS-R used in this thesis, versus measured correlates of aggression, like anger and hostility. Examples of psychiatric diagnostics tests also measuring aggression related symptoms comprise the Positive And Negative Symptom Scale (PANSS)(32) and Brief Psychiatric Rating Scale (BPRS) (33) hostility items.
- self-report measures versus aggression observation-scales

Choice for a specific instrument or combination of instruments depends on the goal of the assessments, which can be: measuring the effect of interventions

but also prediction. Furthermore, the setting and time window of measurement and, in the case of research, the study design (prospective versus retrospective) are likely to influence the choice. Furthermore, practical issues such as available time of researchers and/or clinicians, as well as financial (research) budgets can play a role.

Disadvantages of self-report scales include recall-bias, and tendency of patients to give socially desirable answers (34). In addition, when self-report questionnaires are used to measure changes in aggressive behaviour, a potential lag time between the patients' self-recognition that aggressive behaviour has diminished in frequency and severity and the patients' self-perception that one is still capable of engaging in aggressive acts warrants a longer prospective window of patient assessment (see ***chapter 2.2***). As far as we can judge, preference should be given to the use of observer-rated instruments, especially in inpatients. For outpatients, however, self-report may be the only feasible way to measure aggressive behaviour or aggression-related symptoms.

Measuring aggression related symptoms

The measurement of aggression-related symptoms seems useful when these data are used for prevention in clinical practice, allowing for early intervention in case of high risk of aggressive behaviour. An example of an instrument measuring aggression related symptoms and used for prevention is the Brøsset Violence Checklist (35). Another (practical) reason for using such instruments may be a lack of study power to detect aggressive behaviour. One could think of a short study period and/or a study population consisting of patients with a low incidence of aggression where most patients will be classified as non-aggressive when not displaying actual aggressive behaviour. When measuring aggression related symptoms, more differentiation can be made. Finally, especially in retrospective studies, scales like the PANSS or BPRS may be the only available measures.

Measuring aggressive behaviour

Instruments measuring actually occurring aggressive behaviour can basically be divided into period based observation scales -including the Social Dysfunction and Aggression Scale (36) and the modified version of the Overt Aggression Scale (MOAS) (37)- and incident-based observation scales -including the Staff Observation Scale-Revised used in this thesis (38) and the first version of the OAS (39). Disadvantage of incident-based observer scales is that they are prone for underreporting as was shown in ***chapter 3.1***. We especially expected underreporting of verbal aggressive incidents, assuming that these incidents occur more frequently and may have less impact compared to physical aggressive behaviour. However, the observed underreporting appeared to be non-selective with respect to the severity of the aggressive incidents. Clearly, the staff does experience verbal aggression as being

important as physical aggression, and we feel it is important not to restrict aggression measurement to physical aggression if it is possible to record both.

With period based observation scales, underreporting is less likely to occur. However, recall-bias may be more likely to occur. Another limitation of a period based observer scale is that it does not allow for an accurate investigation of time relationship between the occurrence of aggressive incidents and interventions, as we did in ***chapter 3.2 and 3.3***. Furthermore, it hampers analysis of the context of aggressive incidents, e.g. the provocation but also time of occurrence and used interventions cannot be derived from such a scale, whereas the SOAS-R allows for that. In clinical practice such information is important as it can give clues of factors influencing the occurrence of aggression on the individual patient level.

How has the (type of) measurement of aggression for this thesis influenced the study outcomes?

In this thesis, we measured aggression prospectively with the SOAS-R on three different wards during 15 months. The length of measuring may partly explain the rather high percentage of patients in our study population (60%) displaying aggressive behaviour compared to other shorter studies on acute psychiatric wards in which lower percentages were reported (40). With the SOAS-R being an incident based aggression observation scale, we were able to investigate the temporal association of aggression with medication changes and the administration of as-needed medication (see ***chapter 3.2*** and ***3.3***). It also allowed us to divide patients into severely and mildly aggressive patients based upon the type of aggressive behaviour, which was based upon means used (verbal versus physical aggression) and the consequence. As mentioned earlier, however, a limitation of this method is the underreporting. Despite the underreporting, it appears the SOAS-R was a valid method to roughly divide patients into aggressive and non-aggressive, as in ***chapter 3.1*** we found that for 87% of all patients with aggressive behaviour as reported in the daily reports, at least one aggressive incident was recorded with the SOAS-R. However, the underreporting has affected our results in the sense that we cannot be sure whether the observed increased number of medication changes during the aggression-free follow-up time of aggressive patients compared to the number of changes for non-aggressive patients in ***chapter 3.2*** is a real effect or an overestimation.

In ***chapter 3.4*** investigating patients' and nurses' beliefs about as-needed medication, aggression was measured retrospectively by using the daily reports of nursing staff, which are used for transference of information between shifts. Using daily-reports also can result in underreporting as shown in ***chapter 3.1,*** although we found the amount of underreporting to be lower than using the SOAS-R. This implies that some patients may have been classified wrongly as non-aggressive. We are not sure how this could have affected our study results.

Our hypothesis is that the management or treatment of aggressive behaviour is reactive and in the following paragraph we will substantiate this, for the pharmacological management of aggressive behaviour in particular, by means of the study results presented in this thesis and available literature.

In a broad sense the reactive character of the management of aggressive behaviour is reflected in the (lack of) official guidelines concerning aggressive behaviour. For the major psychiatric disorders, diagnostic procedures, treatment and treatment evaluation are embedded in protocols defining good clinical practice However, in the Netherlands, for example, the only available official guideline in relation to aggressive behaviour is a guideline dealing with coercive measures. In the UK, NICE issued a guideline dealing with short-term management of aggressive behaviour, which provides strategies on how to intervene in the acute situation by addressing short-term risk assessment, interventions and general ward safety issues, including training. Long-term management is not addressed.

The lack of long-term management strategies of aggressive behaviour on a patient-level in guidelines is likely to be a result of the limited evidence base for interventions. We showed that the evidence for the pharmacological management of acute aggression is based upon 19 trials, of which the study population often was small (see ***chapter 2.1***). For the long-term management of aggressive behaviour only weak evidence is available (see ***chapter 2.2***). This limited evidence base for pharmacological management in particular and other interventions in general makes it impossible to draw strong evidence-based conclusions.

In clinical practice, reactive management is observed in ***chapter 3.3,*** in which we investigated the use of as needed medication by aggressive patients. In this study we did not only find that aggressive patients have an increased use of as needed medication (both sedatives and analgesics) compared to non-aggressive patients, but what is more, we found an increased number of administrations in the three hours following an aggressive incident.

In ***chapter 3.2,*** we showed that in clinical practice the reactive management of aggressive behaviour not only concerns short-term interventions like restraint and acute sedation. Regular medication regimens of aggressive patients also appeared to be frequently subject of change. Furthermore, more medication changes took place around aggressive episodes compared to aggression free episodes.

The reactive character of aggression management can probably be explained by the impact of aggressive behaviour; it seems plausible that difficult behaviour such as aggression calls for action. In case of acute aggressive behaviour, sedation of a patient might be rational with the aim of preventing further escalation of the aggressive behaviour. However, available research and studies in this thesis suggest that reactive management is not always rational. An example of irrational prescribing behaviour is that aggressive patients use more psychotropics in their regular

medication regimen, compared to non-aggressive patients (41, 42) despite the lack of evidence for pharmacological maintenance treatment of aggression. Furthermore, in ***chapter 2.3***, oxazepam was the most frequently used as needed medication. Considering that the T_{max} of oxazepam is between two and four hours following administration, medication with a shorter T_{max} like midazolam seems more appropriate. As a recent review about as needed medication shows that the choice of drug differs between typical antipsychotics, benzodiazepines and antihistamines (43), we hypothesize that administering as needed medication has to do with the need of clinicians to act when faced with aggressive behaviour. In that case, the prescriber is likely to base his choice of drug upon local policies and/or the clinicians' preference and experience, rather than evidence-based medicine. Besides the need of clinicians, the administration of as needed medication seems to fulfil a need of the patient too as shown in ***chapter 3.4***. If both patient and staff seem to be satisfied why change or criticise these practices? What we are concerned about, is that (long-term) evaluation of as needed medication practices is sparse, or even lacking, not just in our study population, but also in general (44). We assumed this lack of evaluation to be part of the reactive character of handling: both staff and patients are satisfied when after the administration the aggressive behaviour stops or does not further escalate, and the intervention is assumed effective. Whether the intervention really had an effect or whether the patient would also have calmed down without the medication does not seem important anymore.

With regard to long-term management, the lack of evaluation is a bigger concern as psychotropics used for the long-term management of aggression – mainly antipsychotics, antidepressants and anticonvulsants- have more side effects compared to benzodiazepines used in the acute situation. A similar situation occurred years ago when hyoscine was used frequently to manage aggressive behaviour, despite the well-known and apparently ignored side effects including hallucinations and depression. More recently, in 2005, the FDA warned that with an approximately 1.6-1.7 fold increase in mortality, the use of atypical antipsychotics for the elderly with dementia is a risk (45). In 2008, it became clear that this warning should be applied to all antipsychotics(46). Prescription behaviour of antipsychotics for behaviour problems in elderly with dementia, however, did not change (47). This is remarkable, taking into account the limited effect of antipsychotics on behavioural problems in elderly with dementia. Recently, Kleijer et al, e.g. showed an improvement of behavioural problems for only one on six elderly patients treated with antipyschotics, where withdrawal of antipsychotics was successful in 58% (48).

The latter brings on another concern about the long-term treatment of behavioural problems with psychotropics: the continuation of psychotropics even if they are not effective. For this we also refer to the last study, ***chapter 3.5***. In that study we showed that patients with both aggressive behaviour and using two or more psychotropics are at highest risk for having a negative treatment outcome.

As stated in that chapter it is unclear whether the behaviour would change when less medication would be given. However, we strongly have the impression that all too often tapering the use of medication is not taken into consideration, and if it is, clinicians are reluctant to do so, remembering previous aggressive incidents and fearing worsening of the situation. Finally, this implies that the need to act in case of aggressive behaviour and this fear to taper medication can result in patients using more and more medication.

Recommendations for improvement

To come to a more rational, evidence-based management of aggressive behaviour, more evidence about effective interventions is required. Here we will focus on what is needed to obtain evidence for the pharmacological management of aggression. Randomized controlled trials are still considered the gold standard to obtain evidence. In the case of aggression there are several important subjects researchers should take into account. First, consensus about the concept of aggressive behaviour is needed. This is not only needed to select patients for study inclusion. As we stated previously, regulatory agencies, i.e. the FDA and the EMEA, are only likely to register medication for the management of aggression if consensus about the concept exists among the clinical and academic field. A possible first step to reach this might be to cluster different types of aggressive behaviour in the DSM as described previously. For study inclusion, a certain level of baseline aggression is required. When baseline aggression is low –as was the case in some trials included in our review (***chapter2.2)*** – a long study period is required to reliably detect a reduction of aggressive behaviour. Subsequently, good measurement is important; the use of both an incident-based scale and period based observation scales will likely obtain the most valid results. In ***chapter 2***.3, we showed that a large amount of patients would not be eligible in a typical trial due to the used in- and exclusion criteria. Therefore to obtain results that are generalizable to daily clinical practice, it is important to pay special attention to the used in- and exclusion criteria. With previous research showing a strong link of substance abuse with aggressive behaviour, this should not be used as an exclusion criterion, as is quite common in RCTs. Furthermore, one should seriously consider whether the patient's main DSM disorder should be stable or not for study inclusion. Reason for this is the association of acute mental illness with aggressive behaviour. If during the trial period remission of acute symptoms occurs, it would be difficult to assess if a possible reduction in aggressive behaviour is due to the drug under investigation or to the remission. In summary, conducting such randomized controlled trials may be feasible, but certainly not simple. We, therefore assume that evidence for the management of aggression based upon randomized controlled trials will not appear that soon. However, RCTs are not the sole source for evidence based medicine. Practice based-evidence can be found in pragmatic trials, i.e. trials measuring the benefit a treatment produces in routine

clinical practice. In such trials mostly two different treatments are compared(49). The treatment response is the total difference between two treatments, including both treatment and associated placebo effects, as this will best reflect the likely clinical response in practice (50). Besides pragmatic trials, well-designed observational research can provide valuable practice-based evidence. One could think, e.g. of the current introduction in many health settings of routine measurement of treatment outcome with instruments like the HoNOS, or aggression incidents with instruments like the SOAS. Combining this information with hospital medication and administration databases creates opportunities to conduct large-scale observational studies measuring effectiveness of treatment are provided.
In these last paragraphs strategies for more preventive and rational acting in clinical practice will be discussed. In general, to act more in a preventive and rational way, clinicians should be aware of the course of aggressive behaviour of individual patients. Defining patters can give clues about context of aggressive incidents and give clues for prevention.

Besides the identification of potential triggering factors, monitoring is useful to evaluate interventions used. From a practical point of view this could be achieved by measuring aggressive behaviour. Not only the monitoring of aggressive behaviour is required, but also the monitoring of applied interventions, including coercive measures, and maybe also interventions such as having a walk with the patient in case of agitation. Considering the high pressure of work and the observation on psychiatric wards that a large percentage of aggressive incidents is caused by a small percentage of patients (51), such monitoring could be restricted to these repetitively aggressive patients. Risk factors like previous violence and substance abuse could be used to identify those patients. Additionally, the occurrence of frequent changes in regular medication, as shown in ***chapter 3.2***, may be used for this purpose, especially on long-stay wards. Combining the monitoring of both aggressive behaviour and used interventions can give insight into what is effective and what is not effective for the individual patient. If interventions like pharmacological maintenance treatment are not effective they should be discontinuated.

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Summary

Aggressive behaviour is an important problem in mental health care. Aggressive behaviour does not only affect staff and other patients, but also has a negative impact on the patient self. Studies have shown that aggressive patients have a longer stay on psychiatric wards compared to non-aggressive patients. In psychiatric wards, several interventions are used to manage aggressive behaviour. In the Netherlands, seclusion has for decades been a highly common intervention to manage (imminent) aggression. During recent years, however, the use of seclusion has been heavily criticized. Pharmacotherapy is another commonly used intervention, which is viewed by many as a potential alternative for the management of aggressive behaviour.

In ***chapter 1*** a historical overview of aggression management is provided. Overall, it appears that the interventions used in case of aggressive or disruptive behaviour can be classified into three main categories: restricting freedom of movement (either by seclusion or mechanical restraints), the use of pharmacologically active substances, and a variety of more behavioural and interactional approaches. Furthermore, history shows that some therapies like prolonged bathing and insulin coma, initially deployed with the idea that they have healing properties, kept on being used even after they were shown to be ineffective. Reason for keeping on using these measures was to manage difficult behaviour like agitation and aggression through restriction. When the historical background is not taken into account, it is difficult to understand how caretakers could be convinced of the efficacy and rationality of such interventions. Nowadays, the importance of evidence-based treatment is highly emphasized in medicine. The question is, however, whether current management of aggressive behaviour is more evidence based given the lack of proper studies into the effects of interventions on aggressive behaviour.

The aim of this thesis is to examine the scientific rationale for the pharmacological management of aggressive behaviour, and juxtapose that against clinical practice. We therefore conducted systematic reviews of existing literature and observational studies on psychiatric wards specialized in externalizing behaviour disorders.

In ***chapters 2.1 and 2.2***, we systematically searched the literature for randomized controlled trials (RCTs) investigating the pharmacological management of aggression. In ***chapter 2.1*** we focused on the treatment of aggressive behaviour in the acute situation, while in ***chapter 2.2*** we investigated the maintenance treatment of aggressive behaviour. For the acute situation, both benzodiazepines and antipsychotics appeared to be effective. However, the selected RCTs have important methodological limitations, including small study samples, short study durations and strict in-and exclusion criteria. The same methodological limitations were observed in RCTs investigating the maintenance treatment of aggression. Only weak evidence for anti-aggressive effects of antipsychotics, antidepressants, anticonvulsants, and β-adrenergic–blocking drugs in maintenance treatment was found. Especially in ***chapter 2.2*** we observed that patients enrolled in RCTs differ greatly from psychiatric patients that are seen in clinical practice for whom aggression is a severe problem. In ***chapter 2.3*** we quantified this by applying inclusion and exclusion criteria used in the RCTs to the 106 aggressive psychiatric patients in our study sample. Results show that only 30% to 46% of aggressive psychiatric patients as seen in clinical practice would be eligible to participate in a typical randomized controlled trial based on the most frequently applied exclusion criteria. The comparability of RCTs to clinical practice, and probably also the generalizability, therefore is judged to be low.

In ***chapter 3*** medication patterns in relation to aggressive behaviour were investigated on psychiatric wards. To measure aggressive incidents, the Staff Observation Aggression Scale-Revised (SOAS-R) was used. Because previous literature suggests that the use of the SOAS-R may lead to underreporting of aggressive incidents, the underreporting phenomenon was investigated by comparing SOAS-R recorded incidents with incidents reported in the daily reports of the hospital (***chapter 3.1***). About 30% of the incidents documented in the staff reports were also documented in the SOAS-R. The other way around, however, we showed that a substantial proportion of incidents reported in the SOAS-R (40%) were not documented in the daily staff reports. The proportions of mild incidents (verbal aggression) and severe incidents (physical aggression) were the same for both methods. Thus, although underreporting does occur when using the SOAS-R, this underreporting appears to be non-selective, at least for the severity of the aggressive incidents.

Despite limited evidence for effectiveness of pharmacological treatment of aggressive behaviour, observational studies in this thesis showed that aggressive patients in daily clinical practice use more medication compared to non-aggressive patients. In ***chapter 3.2*** we found that, for aggressive patients, new psychotropics were started more frequently, and dosages were more likely to be increased, compared to non-aggressive patients (Incidence-density ratio [IDR]

1.8, 95% confidence interval [CI] 1.2-2.6 and 2.1; 95% CI 1.4-3.1, respectively); IDs for other changes were non-significantly increased. Furthermore, within the group of aggressive patients, more medication changes were observed in the period of one day before until one day following aggressive episodes, compared to the remaining aggression-free follow-up time (IDR= 2.5; 95% CI 2.0-3.1). We concluded that difficult behaviour such as aggression, triggers reactive prescribing behaviour. In ***chapter 3.3*** we found that aggressive patients have an increased use of both psychotropic and somatic as-needed medication (IDR, 2.5; 95% CI, 2.2 – 2.7 and IDR, 2.1; 95% CI, 1.8 – 2.4, respectively). In the three hours following aggressive incidents, more as-needed medication was administered, compared to the period previous to aggressive incidents. To gain more insight into the reasons for the observed increased use of as-needed medication by aggressive patients, semi-structured interviews with patients and nursing staff, were conducted within 24 hours after an as-needed medication administration (***chapter 3.4***). In this study, aggressive behaviour was measured through daily nursing reports. In the interviews with the patients, it was explored who took the initiative for the administration of as-needed medication (patient versus nurse), the reasons for administration, and the effects of medication. Identical questions were asked to nurses who had administrated the medication. For severely aggressive patients, compared to non-aggressive patients, medication was more frequently administered on the basis of the nurse's initiative (instead of the patient's initiative) (48 versus 19%, respectively, p=0.02). Interestingly, the perceived time of onset of effect of medication was significantly shorter in the perception of the patients compared to the nurses. We hypothesized that apart from pharmacological effects there also appears to be a placebo-effect. Overall, we concluded that the administration of as-needed medication seems to fulfill certain needs of both patients and staff. The question remains whether use of as-needed medication is desirable. An advantage of use of as-needed medication could be that patients use less medication when it is administered on as-needed medication instead of on regular basis. On the other hand we wondered whether use of as-needed medication could possibly lead to a vicious circle in some patients: (physical) violence leads to the administration of more as-needed medication, in this study mainly benzodiazepines. Patients are satisfied with this practice, which thus may to a certain extent reinforce displaying aggressive behaviour.

In ***chapter 3.5*** we investigated the association between aggressive behaviour and psychotropic use on the one hand, and treatment outcome of hospitalized psychiatric patients on the other. Treatment outcome was defined as a transfer to a more open (positive outcome) or a (more) closed ward (negative outcome). Aggressive patients using psychotropic polypharmacy were at highest risk for a negative treatment outcome (Odds ratio 7.6; 95%CI 2.0-29.9;

reference = patients without aggression, without polypharmacy) Results were adjusted for age, sex and diagnosis. A study limitation was that we could not adjust for the severity of illness within diagnoses, which could also be a reason for negative treatment outcome. Overall, as psychotropic polypharmacy does not seem to positively influence treatment outcome and considering the lack of evidence for the pharmacological management of aggression, cautiousness is recommended for the pharmacological management of aggression, and with multiple psychotropic agents in particular..

In ***chapter 4*** the results are discussed in a broader perspective. Although both in clinical and academical field people agree that aggression poses a pro-blem, there is far less consensus about the concept of aggressive behaviour and the way to measure it. More uniformity is required, both for clinical practice and for future research. A way to reach this is more (systematic) attention for aggressive behaviour, which may be reached by including aggressive behaviour in the DSM.

Considering the lack of evidence for the (pharmacological) management of aggressive behaviour it is strongly recommended for daily practice to record aggressive behaviour during admission. Such registrations will facilitate the evaluation of the effects of (pharmacological) interventions aimed at reducing aggression. Furthermore analyses of patterns of aggression of individual patients may provide clues for the treatment and management of aggressive behaviour.

Samenvatting

In de psychiatrie is agressie een belangrijk probleem. Naast de impact die het heeft op medewerkers en medepatiënten, heeft agressie ook negatieve gevolgen voor de patiënt zelf, bijvoorbeeld door de toepassing van drang en dwang. Binnen de psychiatrie worden verschillende interventies toegepast ter behandeling of beheersing van agressie. Van deze interventies staat met name separatie de laatste jaren sterk ter discussie: in GGZ instellingen wordt alles in het werk gesteld om het gebruik van separatie tot een minimum te beperken of zelfs helemaal uit te bannen. Farmacotherapie is een van de andere veelgebruikte interventies voor de beheersing en behandeling van agressie.

In ***hoofdstuk 1*** wordt een overzicht gegeven van de interventies die ingezet worden bij agressie door de jaren heen. Grofweg kan daarbij een onderscheid gemaakt worden tussen maatregelen zoals separatie en fixatie die de bewegingsvrijheid belemmeren, medicatie en gedragsmatige benaderingen. Een aantal interventies, zoals bed- en badtherapie en insuline coma, die aanvankelijk genezing dan wel behandeling van psychiatrisch ziektebeelden beoogden bleken al snel ineffectief. Ze werden echter wel jarenlang toegepast waarbij de focus van de deze interventies niet zelden verschoof van behandeling naar beheersing van gedragsproblemen en agressie. Met de komst van antipsychotica in de jaren 50 in de vorige eeuw leek er aanvankelijk rust te komen op de afdelingen, zo wordt in de literatuur over de zogenaamde 'Largactil-rust' gesproken. Terugkijkend naar de geschiedenis van de psychiatrie lijken veel behandelmethoden uit het verleden nu irrationeel. De vraag is echter of in het huidige tijdperk waarin evidence-based medicine hoog in het vaandel staat, de behandeling van agressie daadwerkelijk rationeler is geworden. Doel van dit proefschrift, is het onderzoeken van de wetenschappelijke onderbouwing voor de medicamenteuze behandeling van agressie, en het in kaart brengen van medicatiegebruik van opgenomen agressieve patiënten in de dagelijkse praktijk. Dit deden we aan de hand van systematische reviews van de bestaande literatuur en een aantal empirische studies binnen afdelingen in een psychiatrische instelling gespecialiseerd in gedragsstoornissen.

In de ***hoofdstukken 2.1 en 2.2***, hebben we in literatuurdatabases systematisch gezocht naar gepubliceerde randomised controlled trials (RCTs) die de farmacotherapeutische behandeling van agressie bestuderen; in ***hoofdstuk 2.1*** betreft het de behandeling van agressie in de acute situatie, in ***hoofdstuk 2.2*** de onderhoudsbehandeling van agressie. Voor de acute behandeling van agressie lijken zowel benzodiazepines als antipsychotica effectief. Er valt, methodologisch gezien, echter veel aan te merken op de kwaliteit van de onderzoekingen naar acute behandeling van agressie: kleine groepsgroottes, korte onderzoeksduur en vaak strenge in- en exclusie criteria waardoor veel cliënten met wie we in de praktijk van alledag te maken hebben buiten de boot vallen. Deze beperkingen gelden ook voor de trials die de effectiviteit van de langdurende medicamenteuze behandeling van agressie onderzoeken. Veel verschillende middelen zijn onderzocht op werkzaamheid voor de langdurende medicamenteuze behandeling van agressie, waarbij de evidentie steeds matig blijkt te zijn. Met name op basis van ***hoofdstuk 2.2*** concluderen wij dat de patiënten-populaties die in RCTs geïncludeerd worden, op een aantal wezenlijke punten niet overeenkomen met de populatie van patiënten die in de praktijk behandeld worden en bij wie agressiviteit daadwerkelijk een groot probleem is.

In ***hoofdstuk 2.3*** hebben we dit verschil tussen de RCT populatie en de dagelijkse praktijk populatie gekwantificeerd door de gebruikte in- en exclusiecriteria van de RCTs toe te passen op de 106 agressieve patiënten uit onze psychiatrische praktijkpopulatie. De resultaten laten zien dat maximaal 50% van de onderzochte patiënten uit de dagelijkse praktijk in aanmerking komt voor deelname aan een RCT die de effectiviteit van psychofarmaca ter behandeling van agressie onderzoeken. Dit percentage ligt feitelijk waarschijnlijk nog lager, omdat er in de meeste RCTs gekeken wordt naar ambulante patiënten, terwijl veel patiënten in dit onderzoek vaak jarenlang zijn opgenomen. Onderzoeksresultaten van RCTs waarin de medicamenteuze behandeling van agressie wordt onderzocht lijken dus slechts beperkt gegeneraliseerd te kunnen worden naar klinische patiënten in de dagelijkse praktijk.

In ***hoofdstuk 3*** hebben we het gebruik van medicatie in relatie tot agressie onderzocht. Om agressie te meten hebben we gebruik gemaakt van de Staff Observation Aggression Scale-Revised (SOAS-R). Omdat in de literatuur wordt gesuggereerd dat het gebruik van de SOAS-R kan leiden tot onderrapportage, hebben we dit onderzocht door de geregistreerde SOAS-R incidenten naast de dagrapportages te leggen (***hoofdstuk 3.1***). Uit de dagrapportages werden inderdaad meer agressieve incidenten gescoord; ruim 70% van de agressieve incidenten in de dagrapportages waren niet geregistreerd met de SOAS-R. Tegelijkertijd was ruim 40% van de SOAS-R incidenten niet terug te vinden in de dagrapportages. Daarnaast was de verhouding tussen milde agressieve inci-

denten (verbaal) en zware agressieve incidenten (fysiek) wel dezelfde bij beide methodes. Hoewel er dus wel sprake is van een onderrapportage, is deze niet selectief voor de ernst van het incident.

Ondanks de geringe wetenschappelijke onderbouwing voor de farmacotherapeutische behandeling van agressie, bleek uit de observationele studies dat agressieve patiënten in de praktijk meer medicatie krijgen dan niet agressieve patiënten. Zo vonden wij in ***hoofdstuk 3.2*** dat starten van nieuwe medicatie en dosisverhogingen significant vaker voorkomen bij agressieve patiënten (Incidentie-dichtheid ratio [IDR] respectievelijk 1,8; 95% betrouwbaarheidsinterval [BI] 1,2-2,6 en 2,1; 95%BI 1,4-3,1). De overige medicatiewisselingen bleken niet significant vaker voor te komen. Daarnaast vonden we dat meer medicatiewisselingen plaatsvinden rondom agressieve incidenten dan tijdens de agressie-vrije periodes van agressieve patiënten (IDR 2,5; 95%BI 2,0-3,1). Wij concludeerden dat moeilijk gedrag zoals agressie leidt tot veranderingen in het gebruik van medicatie. In ***hoofdstuk 3.3*** vonden wij dat agressieve patiënten ook meer zonodig medicatie gebruiken -zowel sederende medicatie als pijnstillers- dan niet agressieve patiënten (IDR respectievelijk 2,5; 95%BI 2,2-2,7 en 2,1; 95%BI 1,8-2,4). Daarnaast bleek dat er in de drie uur volgend op het agressieve incident, de meeste medicatie gegeven werd. Om meer inzicht te krijgen in de redenen van verhoogd gebruik hebben we, zoals beschreven in ***hoofdstuk 3.4***, semi-gestructureerde interviews afgenomen bij patiënten die binnen de voorafgaande 24 uur zonodig medicatie hadden gekregen. Agressie werd in dit onderzoek gemeten door gebruik te maken van de dagrapportages. Er werd onder andere gevraagd op wiens initiatief de medicatie gegeven was, waarom de medicatie gegeven was en wat het effect van de medicatie was. Dezelfde vragen werden ook aan de verpleging gesteld. Het initiatief tot gebruik van medicatie blijkt niet (alleen) vanuit de verstrekkers (verpleging) te komen maar juist vooral vanuit de patiënt zelf. In de groep van de fysiek agressieve patiënten kwam het initiatief voor het geven van zonodig medicatie wel vaker vanuit de verpleging in vergelijking met de groep van niet-agressieve patiënten ($p=0,02$). Opvallend was dat patiënten, vaker dan verpleging een snel effect van de medicatie bemerkten (binnen 15 minuten). Naast het farmacologisch effect lijkt zonodig medicatie ook een placebo-functie te hebben. Uit deze studie concludeerden we dat zonodig medicatie voorziet in een behoefte van zowel patiënten als verpleging. Het blijft de vraag of het gebruik van zonodig medicatie wenselijk is. Een voordeel zou kunnen zijn dat patiënten per saldo minder sederende medicatie gebruiken wanneer het zonodig gegeven wordt dan wanneer het op reguliere basis gegeven wordt. Anderzijds vragen we ons af of er ook een vicieuze cirkel kan ontstaan: patiënten vragen vaak zelf om zonodig medicatie en bij (ernstig) agressieve patiënten wordt het vaker op ini-

tiatief van de verpleging gegeven, de vraag is of dit agressief gedrag zou kunnen bekrachtigen.

In ***hoofdstuk 3.5*** hebben we de relatie tussen agressie en medicatie enerzijds en de uitkomst van behandeling anderzijds onderzocht. De behandeluitkomst werd gedefinieerd als overplaatsing naar een meer open (positieve uitkomst) of gesloten afdeling (negatieve uitkomst). Patiënten die tijdens de studie periode niet werden overgeplaatst en minimaal 6 maanden opgenomen waren hadden ook een negatieve behandeluitkomst. We toonden aan dat agressieve patiënten met veel medicatie het meest vaak een negatieve behandeluitkomst hadden ten opzichte van de patiënten zonder agressieve incidenten en met weinig medicatie (Odds Ratio 7,6; 95%BI 2,0-29,9). Deze uitkomst is gecorrigeerd voor diagnose, leeftijd en geslacht. Een beperking van deze studie was dat we niet konden aantonen of deze resultaten direct met agressief gedrag samenhangen of mogelijk (ook) verklaard kunnen worden door de ernst van de ziekte. We concludeerden dat het gebruik van veel medicatie niet leidt tot een betere behandeluitkomst, ook al weten we niet of het nog slechter met de "agressieve patiënten" zou gaan als ze minder medicatie gebruiken. Gezien deze resultaten, alsmede de bijwerkingen die geneesmiddelen kunnen veroorzaken en de eerder gevonden beperkte wetenschappelijke onderbouwing voor de medicamenteuze behandeling van agressie, stellen we daarom dat goede evaluatie van medicatie(additie) noodzakelijk is.

In ***hoofdstuk 4*** worden de resultaten in breder perspectief besproken. Hoewel agressie binnen de psychiatrie in het algemeen gezien wordt als een belangrijk probleem, is er onvoldoende consensus over de definitie en hoe agressie te meten. Dit gebrek aan consensus is een belemmering voor onderzoek naar, maar ook voor behandeling van agressie in de praktijk. Wij stellen daarom dat er meer consensus over het concept agressie en het meten daarvan bereikt moet worden. Een manier om dat te bereiken is meer (sytematische) aandacht voor agressie; gedacht kan worden aan het opnemen van agressie in de DSM.

Gezien de geringe wetenschappelijke onderbouwing van de medicamenteuze behandeling van agressie wordt ook geadviseerd agressief gedrag tijdens de behandeling te registreren om zo het effect van interventies te kunnen evalueren. Daarnaast kan analyse van agressieregistratie aanknopingspunten geven voor behandeling.

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